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Stereoselective Synthesis of α- and β-L-*C*-Fucosyl Aldehydes and Their Utility in the Assembly of *C*-Fucosides of Biological Relevance

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An efficient synthesis of *O*-benzylated derivatives of the title sugar aldehydes via thiazole addition to tri-*O*-benzyl-L-fuconolactone followed by highly stereoselective deoxygenation of the resulting thiazolylketose and thiazole to formyl transformation is described. Wittig olefination of these aldehydes with galactopyranose and glucopyranose 6-phosphoranes and reduction of the resulting alkenes afforded α- and β-linked (1→6)-L-*C*-fucosyl disaccharides, namely, β-L-*C*-Fuc-(1→6)-α-D-Gal, α-L-*C*-Fuc-(1→6)-α-D-Gal, and α-L-*C*-Fuc-(1→6)-α-D-Glc. The α-anomer of the above *C*-fucosyl aldehydes was transformed into a *C*-fucosylmethyl triphenylphosphonium iodide from which the corresponding *C*-fucosylmethylene phosphorane was generated upon treatment with BuLi. This phosphorane reacted with the Garner aldehyde (*N*-Boc D-serinal acetonide) and its one-carbon higher homologue to give alkenes whose reduction and unveiling of the glycinyl group from the oxazolidine ring afforded *C*-fucosyl α-amino acids, namely α-L-linked *C*-fucosyl serines and *C*-fucosyl asparagines. As a final test of the synthetic utility of the title aldehydes, the β-anomer was employed as starting material in the stereoselective synthesis of both *R*- and *S*-epimer L-*C*-fucosyl phenylhydroxy acetates. One epimer was obtained by reaction of the sugar aldehyde with phenylmagnesium bromide, oxidation of the resulting alcohol to ketone, addition of 2-lithiothiazole to the latter, and transformation of the thiazole ring into the carboxyl group through an aldehyde intermediate. The other epimer was obtained by the same procedure and inverting the timing of phenyl and thiazolyl group addition. In both routes, the key step establishing the configuration of the quaternary carbon atom of the aliphatic chain was the highly stereoselective addition of the organometal to the ketone intermediate.

Introduction

Anomeric sugar aldehydes, namely formyl *C*-glycosides, have been demonstrated in recent years by extensive research carried out in our laboratory[1] to be readily accessible and versatile reactive building blocks for more complex *C*-glycosides, either isosteres of *O*- and *N*-glycoside natural products such as oligosaccharides[2] and glycosyl amino acids[3] or totally artificial (unnatural) compounds such as carbohydrate−heterocycle[4] and carbohydrate−fullerene conjugates.[5] Reports by other groups have appeared as well,[6] thus demonstrating the utility of these compounds as precursors for carbohydrate mimics. Notably, Kishi and co-workers employed properly protected anomeric sugar aldehydes in synthetic routes to *C*-disaccharides and *C*-trisaccharides for conformational studies[7] and Bednarski's group pioneered the synthesis of *C*-glycopeptides using a *C*-glycosyl amino acid, which in turn was prepared from the corresponding formyl *C*-glycoside.[8] The replacement of the exocyclic carbon−oxygen or carbon−nitrogen bond of native glycoconjugates with a carbon−carbon bond creates compounds which are impervious to chemical and enzymatic degradation. Therefore the ready access to *C*-glycoside libraries is of great importance in modern carbohydrate chemistry because *C*-glycosides may serve inter alia as (i) biological probes in glycobiology,[9] (ii) leads for the development of metabolically stable carbohydrate-based therapeutics,[10] and (iii) building blocks for the prepara-

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tion of a variety of biologically important natural products[11]in meaningful amounts and pure state suitable for biomedical studies. Although several syntheses of *C*-glycosides have been reported based on various types of substitution reactions at the anomeric carbon,[12] most of them were scarcely stereoselective as they afforded mixtures of α- and *β*-linked products. An alternative approach that allows this stereochemical problem to be avoided is based on establishing first the required configuration at the anomeric center by the introduction of a carbon functionality and then exploiting the chemistry of this functionality for the construction of the target complex carbon chain. This program was fueled by the effectiveness of a formylation methodology of carbohydrates which allowed the preparation of a collection of formyl *C*-glycosides on a multigram scale and in several cases in both α- and *β*-anomeric forms.[13] The methodology is based on the thiazole-aldehyde synthesis[14] and consists of the addition of lithiothiazole or lithiobenzothiazole to readily available sugar lactones, followed by stereoselective deoxygenation of the resulting thiazolylketose and transformation of the thiazole ring into the formyl group.[15] Wishing to extend the scope of this approach to various *C*-glycosides of special biological relevance, we would like to report here the stereoselective synthesis of the hitherto unknown α- and *β*-L-fucosyl aldehydes α-**1** and *β*-**1** (Figure 1) and demonstrate their synthetic utility in the preparation of three types of *C*-fucosides, i.e., *C*-fucosyl disaccharides, *C*-fucosyl α-amino acids, and

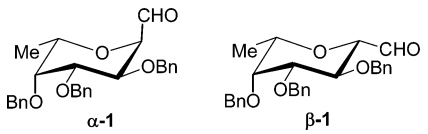

FIGURE 1. *O*-Benzylated α- and *β*-L-linked formyl *C*-fucosides α-**1** and *β*-**1**.

C-fucosyl phenylacetic acids. Fucosylation is very common in nature and it affects significantly the conformation and biological properties of natural glycoproteins and glycolipids. For example, well-known fucose-containing saccharides are sialyl Lewis x (sLe^x) and sialyl Lewis a (sLe^a) of cell-surface glycoproteins and glycolipids. These and other fucosylated oligosaccharide structures play a key role in cell−cell interaction and cell migration phenomena which are involved in vital processes.[16] However, it is well-established that the α-L-linkage of *O*-fucosides is very labile to acids[17] and easily cleaved by glycosidases. Therefore it has been suggested that sLe^x mimics should contain the fucose unit linked throughthe *C*-glycosidic bond to achieve sufficient stability in vivo against fucosidases.[18] For similar reasons, such a type of isosteric variation should be highly beneficial for the stability of the fucosylated trisaccharide *N*-linked to asparagine of CD52 peptides.[19] Another topic of great interest is that regarding the synthesis of *C*-fucosylated tumor-associated carbohydrate antigens to be used in place of *O*-fucosylated analogues for the development of potential vaccines against cancer.[20] Fortunately, despite structural investigations based on comparative NMR studies having revealed notable conformational differences between unnatural *C*-glycosides and natural *O*-glycosides,[21] recent studies have shown that their binding constants and biological properties are very similar.[22]

Results and Discussion

Synthesis of L-*C*-Fucosyl Aldehydes. *O*-Benzylated L-*C*-fucosyl aldehyde anomers α-**1** and *β*-**1** were targeted as suitably protected compounds in synthesis because the benzyl protective group is compatible with a variety of reactions of the formyl group and nevertheless can be easily removed from the final products under neutral conditions by catalytic hydrogenation. Hence the synthesis of α-**1** and *β*-**1** began from known[23] L-fuconolactone **3** (Scheme 1), which in turn was prepared in multigram scale by oxidation of 2,3,4-tri-*O*-benzyl L-fucose **2**.[24] Treatment of **3** in Et_2O at −78 °C with a solution of 2-lithiothiazole (2-LTT, **4**), generated in situ from 2-bro-

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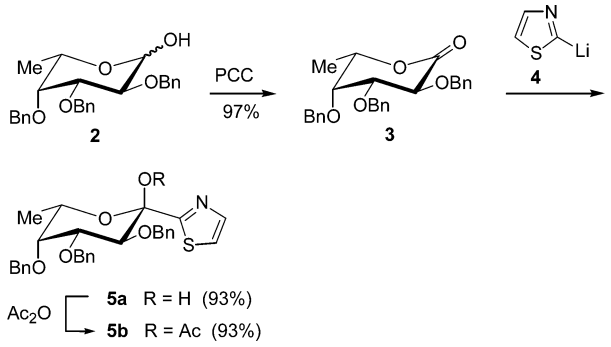
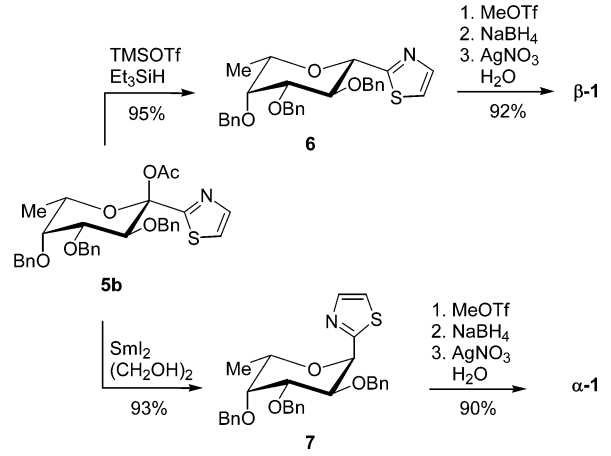
SCHEME 1



SCHEME 2



mothiazole and BuLi, afforded the thiazolylketose **5a** as a single isolated anomer (93%). This compound was acetylated under standard conditions (Ac_2O, Et_3N in CH_2Cl_2) to give the *O*-acetate **5b** as a crystalline product in 93% isolated yield by chromatography. The $^1C_4$ structure of this L-ketoside featuring the α-linked acetoxy group was supported by NMR coupling constant values ($J_{2,3}$ = 10.0 Hz) and nOe experiments showing substantial interactions between the acetyl group and the axial H-3 and H-5 protons. The same structure was assigned to the ketose **5a**.[25] Afterward, compound **5b** was obtained in a preparative useful scale by the above reaction sequence starting from 22.7 mmol (9.87 g) of *O*-benzylated L-fucose **2** and without purification of lactone **3** and ketose **5a**. In a typical procedure, pure compound **5b** was isolated by column chromatography in 92% overall yield.

The next key step toward the stereoselective synthesis of each aldehyde α-**1** or *β*-**1** consisted of removing the acetoxy group from **5b** to give either α-linked or *β*-linked thiazolyl *C*-fucoside, i.e., the configurationally stable and ultimate precursors of the target diastereomeric aldehydes. To this aim, the thiazolylketose acetate **5b** was treated with two different deoxygenative systems, namely the trimethylsilyl triflate−triethylsilane mixture (TMSOTf−Et_3SiH) and the samarium iodide−ethylene glycol mixture (SmI_2−$(CH_2OH)_2$) (Scheme 2). These reagents have been shown in earlier work from our laboratory[26] to give opposite α/*β* selectivities in their reactions with various thiazolylketose acetates. Gratifyingly, also the reductive deoxygenation of **5b** with these reagents showed opposite α/*β* ratios. Specifically the use of TMSOTf−Et_3SiH afforded exclusively the *β*-L-linked thiazolyl *C*-fucoside **6** (95%) whereas SmI_2−$(CH_2OH)_2$ furnished as main product the α-linked isomer **7** (93%) and only 6% of the stereoisomer **6** (Scheme 2). Both reactions were carried out on preparative scale starting from 1 to 3 g of **5b**. The anomeric configurations of these key intermediates, easily established by ^1H NMR analysis,[27] are in agreement with earlier postulated mechanisms of the deoxygenation reactions. In the case of the TMSOTf-promoted reduction, a chairlike transition state[7a] was formed by an axial attack of the hydride ion (from silane) to the anomeric oxycarbenium ion adopting a half-chair conformation. On the other hand, in the case of the SmI_2-induced reaction, the more thermodynamically stable equatorial organosamarium(III) intermediate,[28] formed by a thiazole-assisted two-electron reduction process, underwent a protodesamariation with retention of configuration.

Having constructed both the configurationally stable thiazolyl *β*- and α-*C*-fucosides **6** and **7**, the final operation for the unveiling of the target aldehydes *β*-**1** and α-**1** entailed the transformation of the thiazole ring into the formyl group (Th → CHO) by the highly reliable standard protocol consisting of *N*-methylation (MeOTf), reduction ($NaBH_4$), and hydrolysis (H_2O−$AgNO_3$). Once again this operation turned out to be particularly effective as each crude aldehyde was isolated in high yield (ca. 90%) and sufficiently pure form (ca. 95%) as determined by NMR analysis.[29] The whole unmasking operation required about 2 h and was carried out with identical results on 50 mg up to 1−2 g scale.

Synthesis of L-*C*-Fucosyl Disaccharides. As a first test of the reactivity and synthetic utility of aldehydes α-**1** and *β*-**1** we considered their Wittig olefination by sugar phosphoranes to pave the way for the synthesis of *C*-fucosyl disaccharides.[30] The wide scope of the Wittig-based approach toward the stereoselective assembly of carbohydrate units through a 1,6- or 1,5 ethylene tether[2] and its superior efficiency with respect to the Henry-based methodology employed in other laboratories[31] have been demonstrated by the preparation of a collection of

(25) No studies were carried out to establish whether **5a** is the product of the kinetic or thermodynamic control resulting from the addition of **4** to the lactone **3**. This would require the quenching of the reaction mixture at low temperature with Ac_2O. However, addressing this issue is unimportant in the context of the present work.

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(27) All *β*-L-*C*-fucosides prepared, both benzylated and acetylated, showed in their ^1H NMR spectra large coupling constant values (9−10 Hz) between the H-1, H-2 and H-2, H-3 protons of the pyranose ring, as expected for a trans-diaxial arrangement of these protons ($^1C_4$ conformation). On the other hand, the ^1H NMR analysis of the benzylated α-L-*C*-fucosides indicated that these compounds did not adopt a chair conformation ($J_{1,2}$ = 3−4 Hz, $J_{2,3}$ = 5−7 Hz). However, the corresponding acetylated analogues **15**, **16**, **23**, and **28** showed coupling constant values typical of α-L-configured *C*-fucopyranosides in a $^1C_4$ conformation ($J_{1,2}$ = 5.6−5.8 Hz, $J_{2,3}$ = 10.2−10.3 Hz).

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(29) Compound α-**1** was prepared by Kishi and co-workers (ref 7c) but the physical and spectroscopic data were not reported, whereas *β*-**1** appears to be a new compound to the best of our knowledge.

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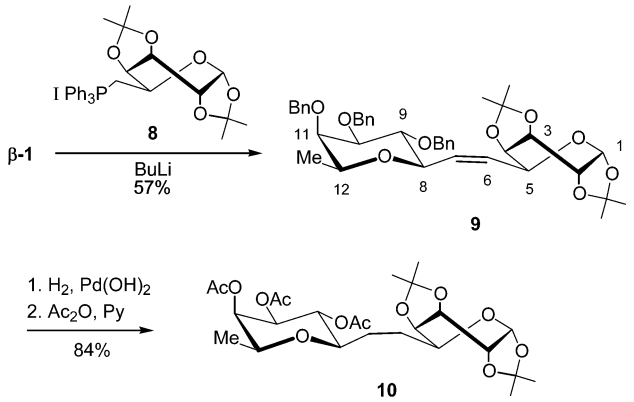
SCHEME 3



C-disaccharides as well as various *C*-oligosaccharides up to a *β*-D-(1→6)-pentamer. Thus, the fucosyl aldehyde *β*-**1** was allowed to react with the acetonide-protected galactopyranose[32] 6-phosphorane generated in situ by treatment of the known[33] phosphonium iodide **8** with BuLi in THF−HMPA at −30 °C (Scheme 3). The reaction afforded the (*Z*)-alkene **9** in fair isolated yield (57%) and whose configuration was established by the corresponding proton coupling constant value ($J_{6,7}$ = 11.5 Hz). More importantly, it was demonstrated that the configurations at C-8 of the fucosyl moiety and C-5 of the galactosyl moiety of **9** were the same as in the coupling reagents *β*-**1** and **8**. Accordingly, the NMR spectrum of **9** showed a $J_{8,9}$ value of 9.5 Hz and a $J_{4,5}$ value of 1.7 Hz.[34] Next, compound **9** was subjected to hydrogenolysis over $Pd(OH)_2$ by which the reduction of the carbon−carbon double bond and the concomitant removal of the benzyl groups were accomplished. Then, the crude product was treated with Ac_2O−pyridine and the resulting *O*-acetyl and *O*-isopropylidene-protected (1→6)-*C*-fucosyl-galactoside (*β*-L-*C*-Fuc-(1→6)-α-D-Gal) **10** was isolated in a rewarding 84% yield.

Given the large diffusion of the native α-*O*-fucosidic linkage in oligosaccharides, the synthesis of α-configured carbon-linked analogues appeared to be quite important. Therefore the fucosyl aldehyde α-**1** was reacted with two α-D-glycopyranose 6-phosphoranes, one derived from the aforementioned galactose phosphonium salt **8** and the other from the recently prepared[2a,b] *O*-benzylated glucopyranose phosphonium iodide **11** (Scheme 4). In both cases the phosphorane generation and the coupling with the sugar aldehyde α-**1** were carried out as outlined in Scheme 3. These Wittig reactions afforded the alkene **12** (48%) and **14** (37%) as 4:1 and 1:1 *Z*,*E* mixtures, respectively. In addition to the desired alkenes **12** and **14**, these reactions produced numerous side products as shown by TLC and NMR analyses of the crude reaction mixtures. One of these products was isolated (7−10%) and characterized as the *C*-formyl glycal **13**. Very likely the reactions of α-**1** with the above sugar phosphoranes were sluggish and therefore base-induced *β*-elimination of the benzyloxy group at C-2 leading to **13** did take place. The alkenes **12** and **14** were elaborated in the usual way, i.e., $Pd(OH)_2$-catalyzed hydrogenation and acetylation, to give the *O*-protected (1,6)-linked *C*-disaccharides α-L-*C*-Fuc-(1→6)-α-D-Gal **15** (80%) and α-L-*C*-Fuc-(1→6)-α-D-Glc **16** (60%). The NMR spectra of both compounds **15** and **16** showed $J_{8,9}$ values of ca. 5.7 Hz in agreement with the α-L-fucosyl linkage and $J_{4,5}$ values of 1.5 and 10.0 Hz consistent with the D-*galacto* and D-*gluco* configuration, respectively.

Synthesis of L-*C*-Fucosyl Amino Acids. Next, we examined the possibility of preparing *C*-fucosyl α-amino acids,[35] especially methylene isosteres of *O*-fucosyl serines[36] and ethylene isosteres of *N*-fucosyl asparagines. The synthesis of *C*-glycosyl α-amino acids can be considered as the gateway to artificial glycopeptides,[37] i.e., a class of glycomimetics of great potential for the control of natural glycoprotein biological activity.[9,38] Also in this endeavor we planned to assemble the fucosyl and amino acid moieties through a carbon−carbon bond generated by a Wittig-type reaction. However, earlier work in our laboratory[39] dealing with the synthesis of *β*-D-*C*-galactosyl L-serine (Gal*β*-CH_2-Ser) demonstrated that the effectiveness of this approach is optimized by coupling an anomeric sugar phosphorane with an aldehyde bearing a masked glycinyl group. Therefore we envisaged the L-fucosylmethyl phosphonium salt **19** as precursor to the desired ylide. This salt was prepared in a few steps and high yield by standard functional group transformations starting from the *C*-fucosyl aldehyde α-**1** (Scheme 5). Succinctly, this aldehyde was reduced ($NaBH_4$) to the alcohol **17** and this product was transformed (PPh_3, I_2) into the iodomethyl derivative **18**. The ^1H NMR spectrum of **18** demonstrated ($J_{2,3}$ = 3.5 Hz) that there was no loss of the α-L-configuration at the anomeric carbon of the fucosyl residue. Finally, treatment of **18** with PPh_3 in the absence of solvent at 120 °C afforded the target phosphonium iodide **19** in 85% overall yield from α-**1**.

The Wittig coupling of the ylide generated in situ from the fucosylated triphenylmethylphosphonium iodide **19**

(31) (a) Martin, O. R.; Lai, W. *J. Org. Chem.* **1993**, *58*, 176. (b) Kobertz, W. R.; Bertozzi, C. R.; Bednarski, M. D. *J. Org. Chem.* **1996**, *61*, 1894. (c) Spak, S. J.; Martin, O. R. *Tetrahedron* **2000**, *56*, 217.

(32) 1,2:3,4-Di-*O*-isopropylidene-D-galactopyranose derivatives do not adopt a chair conformation as proved by the coupling constant values in their ^1H NMR spectra. Moreover, since in the literature there was some confusion concerning the actual conformation of this sugar residue, it is a common practice to draw the structure in a Haworth presentation. However, a very recent study provided evidence that 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose and 6-*O*-glycosylated derivatives adopt a $^0S_2$ conformation in solid state as well as in solution (Roslund, M. U.; Klika, K. D.; Lehtilä, R. L.; Tähtinen, P.; Sillanpää, R.; Leino, R. *J. Org. Chem.* **2004**, *69*, 18). Therefore the di-*O*-isopropylidene-D-galactopyranose moieties presented in this paper are drawn in this conformation.

(33) Secrist, J. A., III; Wu, S.-R. *J. Org. Chem.* **1979**, *44*, 1434.

(34) For all *C*-disaccharidic olefins and the corresponding alkanes the same IUPAC numbering system outlined for **9** was adopted, i.e., counting starts from the reducing end of the disaccharide.

(35) A few syntheses of *C*-fucosyl amino acids have been reported in the literature. *C*-Fucosyl glycines: (a) Jarvest, R. L.; Berge, J. M.; Brown, P.; Hamprecht, D. W.; McNair, D. J.; Mensah, L.; O'Hanlon, P. J.; Pope, A. J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 715. *C*-Fucosyl alanines: (b) Vincent, S. P.; Schleyer, A.; Wong, C.-H. *J. Org. Chem.* **2000**, *65*, 4440. *C*-Fucosyl serines: (c) Sutherlin, D. P.; Stark, T. M.; Hughes, R.; Armstrong, R. W. *J. Org. Chem.* **1996**, *61*, 8350. *C*-Fucosyl *β*-hydroxyserines: (d) Huwe, C. M.; Woltering, T. J.; Jiricek, J.; Weitz-Schmidt, G.; Wong, C.-H. *Bioorg. Med. Chem.* **1999**, *7*, 773.

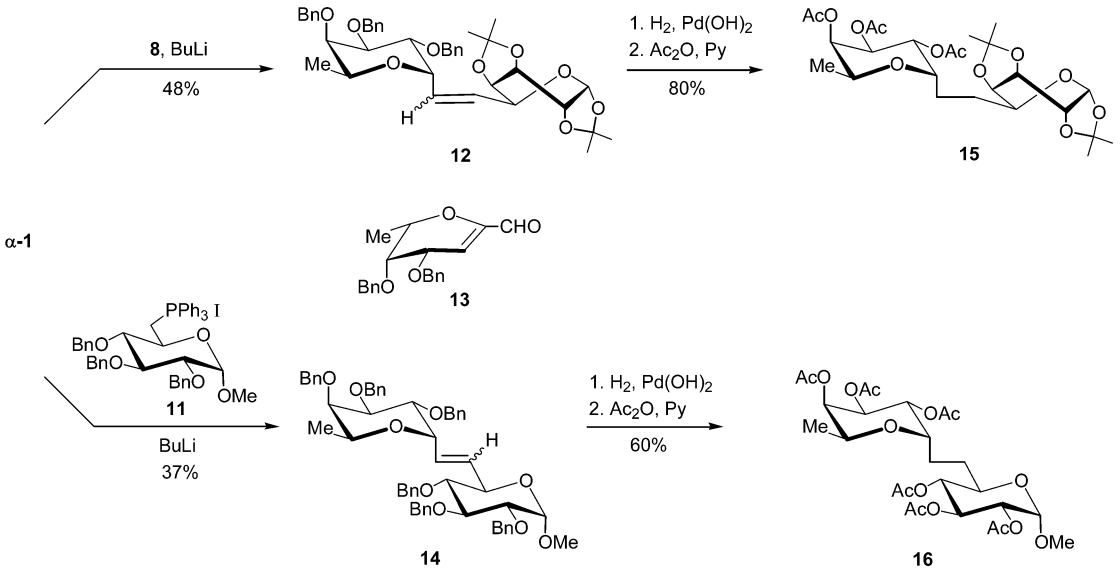
(36) (a) Bjoern, S.; Foster, D. C.; Thim, L.; Wiberg, F. C.; Christensen, M.; Komiyama, Y.; Pedersen, A. H.; Kisiel, W. *J. Biol. Chem.* **1991**, *266*, 11051. (b) Harris, R. J.; Ling, V. T.; Spellman, M. W. *J. Biol. Chem.* **1992**, *267*, 5102. (c) Nishimura, H.; Takao, T.; Hase, S.; Shimonishi, Y.; Iwanaga, S. *J. Biol. Chem.* **1992**, *267*, 17520. (d) Harris, R. J.; van Halbeek, H.; Glushka, J.; Basa, L. J.; Ling, V. T.; Smith, K. J.; Spellman, M. W. *Biochemistry* **1993**, *32*, 6539.

(37) Dondoni, A.; Marra, A. *Chem. Rev.* **2000**, *100*, 4935.

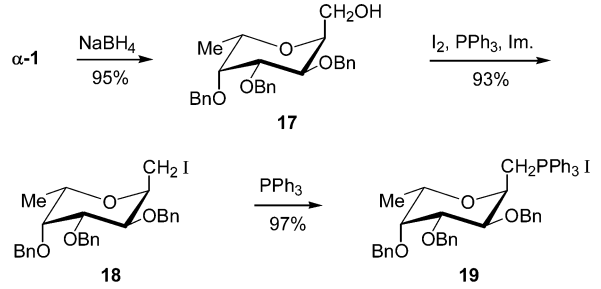
(38) Marcaurelle, L. A.; Bertozzi, C. R. *Chem. Eur. J.* **1999**, *5*, 1384.

(39) Dondoni, A.; Marra, A.; Massi, A. *Tetrahedron* **1998**, *54*, 2827.

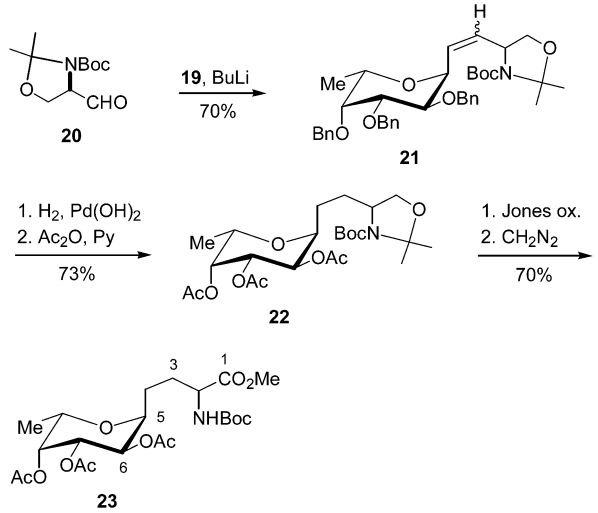
SCHEME 4



SCHEME 5



SCHEME 6



(BuLi, THF−HMPA, 0 °C) was carried out with the well-known α-amino aldehyde[40] **20** (D-serinal) since this reagent contains the masked chiral glycinyl group in the form of the *N*-Boc oxazolidine ring (Scheme 6). We have demonstrated in earlier syntheses of glycosyl amino acids[3,39,41] the advantages associated with the use of amino acid equivalents with the desired absolute stereochemistry already in place.[42] Deceptively, this strategy failed in the present case since under optimized conditions (THF−HMPA, from −20 to 0 °C) the above reaction afforded the alkene **21** (70%) as a 3:1 *E*,*Z* mixture containing *R*- and *S*-configured *N*-Boc oxazolidine rings.[43] Evidently, under the above conditions epimerization did take place at the nitrogenated carbon atom of the oxazolidine ring of **20**. Unfortunately, when milder conditions were adopted such as lowering the temperature to −40 °C, the yields of **21** were in the range of only 15−30% and still substantial epimerization was observed. Pressing forward nonetheless, the mixture of alkenes **21** was duly elaborated by hydrogenation and acetylation to give the mixture of diastereoisomers **22** which in turn was subjected to the one-step oxidative cleavage of the oxazolidine ring by the Jones' reagent (CrO_3, H_2SO_4−H_2O) and esterification by diazomethane. This reaction sequence furnished a mixture of *C*-fucosyl α-amino ester α-epimers **23** in ca. 3:2 ratio by NMR analysis. The same analysis confirmed the α-configuration at the anomeric carbon of the fucosyl residue since $J_{5,6}$ values of 5.6 Hz were observed for both diastereoisomers. These compounds can be considered as α-L-linked fucosyl serine methylene isosteres (Fucα-CH_2-Ser), i.e., analogues of natural *O*-fucosyl serines which are widely distributed in human coagulation factors.[36] Attempts to isolate each individual diastereoisomer by column flash chromatography failed so far. However, the mixture of these compounds can be profitably employed in the synthesis of *C*-fucosylated peptides whose stereoisomers

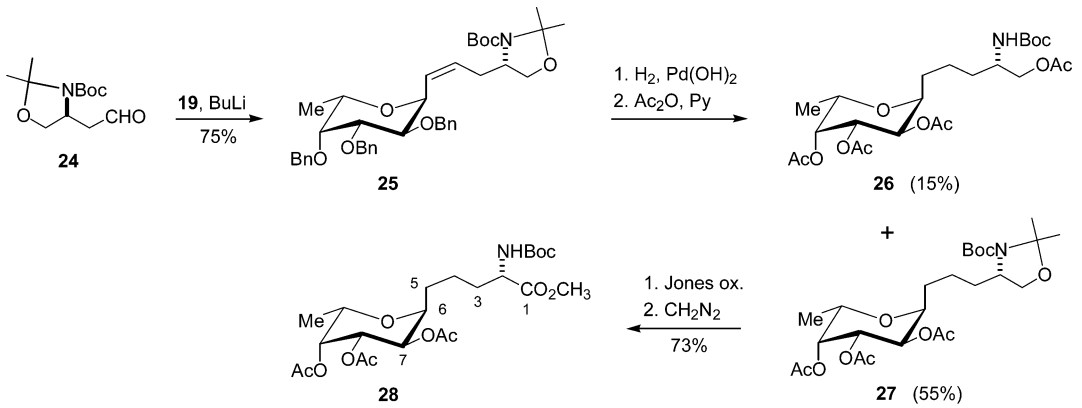
(40) Garner, P. *Tetrahedron Lett.* **1984**, *25*, 5855. For a recent account of the synthetic application of this aldehyde, see: Liang, X.; Andersch, J.; Bols, M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2136. For an improved synthesis avoiding racemization, see: Dondoni, A.; Perrone, D. *Synthesis* **1997**, 527. Dondoni, A.; Perrone, D. *Org. Synth.* **1999**, *77*, 64.

(41) (a) Dondoni, A.; Marra, A.; Massi, A. *Chem. Commun.* **1998**, 1741. (b) Dondoni, A.; Massi, A.; Marra, A. *Tetrahedron Lett.* **1998**, *39*, 6601. (c) Dondoni, A.; Giovannini, P. P.; Marra, A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2380. (d) Dondoni, A.; Mariotti, G.; Marra, A.; Massi, A. *Synthesis* **2001**, 2129. (e) Dondoni, A.; Mariotti, G.; Marra, A. *J. Org. Chem.* **2002**, *67*, 4475.

(42) This simple yet quite useful strategy has been used by other groups. For illustration of reaction schemes and leading references, see ref 37.

(43) The NMR spectra recorded at room temperature of all compounds containing a *N*,*N*-dialkyl-*N*-Boc amine function showed multiple sets of signals arising from the hindered rotation around the σ-bonds. Consistent spectra were obtained in the range 100−160 °C due to the coalescence of signals (see the Experimental Section).

SCHEME 7



can hopefully be more easily separable. There are two precedents on the use of mixtures of *C*-glycosyl serine α-epimers, one dealing with the preparation of decapeptides with potential activity on T-cell stimulation,[44] the other with the synthesis of sialyl Lewis x glycomimetics.[35c]

More rewarding results were obtained by the Wittig olefination of the configurationally stable homoserine derived aldehyde[45] **24** (Scheme 7). Treatment of this aldehyde with the fucosylmethylene phosphorane derived from **19** under the above conditions afforded the alkene **25** as a single *Z*-isomer in 75% isolated yield ($J_{4,5}$ = 11.5 Hz). The $Pd(OH)_2$-promoted hydrogenation of **25** in 1:1 MeOH−AcOEt, followed by acetylation with Ac_2O−pyridine, furnished the tetra-*O*-acetate **26** as the major product. Apparently, opening the oxazolidine ring of **25** did take place in the course of the hydrogenation step, very likely because of some content of acetic acid in the solvent. Thus, exclusion of AcOEt appeared to be advisable. Since **25** was scarcely soluble in MeOH, the hydrogenation was carried out with EtOH as the solvent. The acetylation of the resulting product afforded the ester **26** in low yield (15%) and the desired alkyl oxazolidine **27** in fair yield (55%). The oxidative cleavage of the oxazolidine ring of the latter product with Jones' reagent and esterification furnished the *O*-Ac and *N*-Boc *C*-fucosyl α-amino ester **28**, a suitably protected building block for solid-phase *N*-Boc-based peptide synthesis. The α-fucosyl linkage in **28** and in the precursors **25** and **27** was confirmed by a $J_{6,7}$ value of 5.7 Hz in its ^{1}H NMR spectrum. Thus, the corresponding free amino acid can be regarded as the α-L-linked fucosyl L-asparagine ethylene isostere (Fucα-CH_2CH_2-Asn) although the native *N*-linked analogue has not been reported to the best of our knowledge.

Synthesis of L-*C*-Fucosyl Phenylhydroxy Acetates. The above *C*-fucosyl disaccharides and amino acids belong to families of *C*-glycosides whose convenient synthesis from anomeric sugar aldehydes was previously established. A demonstration of the utility of formyl *C*-glycosides in the synthesis of a new class of *C*-glycosides was undertaken following a recent publication by Pasetto and Franck.[46] These researchers were faced with the nontrivial task of developing a stereoselective synthesis of both epimers of α-D-linked *C*-altrosyl phenylhydroxy acetate **29** (Figure 2). One of these epimers

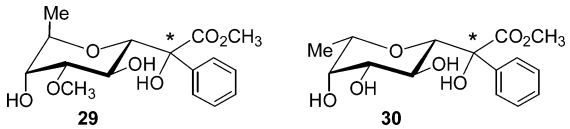


FIGURE 2. Hydroxy- and phenyl-substituted *C*-altrosyl and *C*-fucosyl acetates **29** and **30**.

represents the glycosidic part of the natural antitumor antibiotic Altromycin B. Starting from either D-glucose or D-altrose, Pasetto and Franck succeeded in preparing both (*R*)-**29** and (*S*)-**29** by a rather laborious synthetic sequence. The reaction scheme involved first the synthesis of *S*-glycosides and the Ramberg−Bäcklund rearrangement of their sulfones to set up the *C*-glycosidic linkage. Then, a multistep elaboration of the resulting *exo*-glycals was carried out to build up the chiral phenylhydroxy acetate moieties with opposite configurations. Thus, we were spurred to develop an alternative and expeditious synthesis of *C*-glycosyl phenylhydroxy acetates starting from formyl *C*-glycosides. In particular we focused on the use of the fucosyl aldehyde *β*-**1** as a starting material since this would lead to the C-7 epimer of **29**, i.e., the *C*-fucosyl phenylhydroxy acetate **30** (Figure 2). If successful, this new synthesis would constitute a model route for an alternative approach to **29**. In addition to that, we realized that the synthesis of chiral tertiary alcohols, particularly those bearing complex substituents, was a topic of current interest.[47]

We envisaged the construction of the chiral side chain of **30** by transformation of the aldehyde *β*-**1** into a tertiary alcohol bearing fucosyl, phenyl, and thiazolyl substituents. The heterocycle substituent would serve as a masked formyl group readily transformable into the desired carboxylate. To this aim, *β*-**1** was first reacted with phenylmagnesium bromide in THF at low temperature (−60 to −35 °C) and the resulting mixture of diastereomeric alcohols was oxidized by pyridinium chlorochromate (PCC) to furnish the ketone **31** in 67% isolated yield (Scheme 8). Then, addition of 2-LTT **4** to this ketone in Et_2O−THF at low temperature afforded

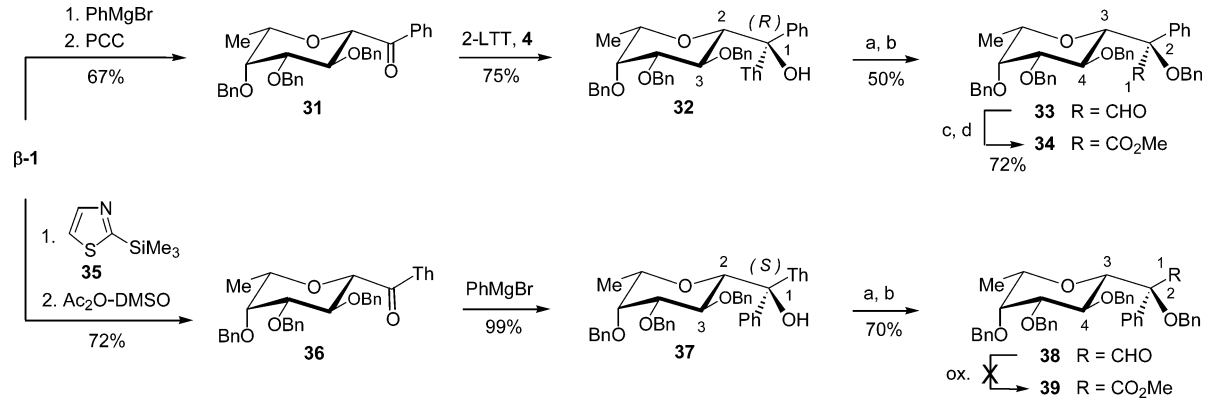
(44) Tedebark, U.; Meldal, M.; Panza, L.; Bock, K. *Tetrahedron Lett.* **1998**, *39*, 1815.

(45) The synthesis of this aldehyde was previously reported but the compound was not characterized by suitable physical and spectroscopic data (Ksander, G. M.; de Jesus, R.; Yuan, A.; Ghai, R. D.; Trapani, A.; McMartin, C.; Bohacek, R. *J. Med. Chem.* **1997**, *40*, 495). An improved synthesis and full characterization of this compound are described in the Experimental Section.

(46) Pasetto, P.; Franck, R. W. *J. Org. Chem.* **2003**, *68*, 8042.

(47) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 284.

SCHEME 8 [a]



[a] Reagents: (a) BnBr, NaH; (b) MeOTf, then $NaBH_4$, then $AgNO_3$, H_2O; (c) Jones' reagent; (d) CH_2N_2.

the tertiary alcohol **32** in 75% isolated yield. The absolute configuration at the newly formed quaternary carbon in this compound was assigned as detailed below. After this stereoselective transformation was carried out, we reasoned that inverting the timing of phenyl and thiazolyl group addition in the above reaction sequence might lead to the epimer of **32**, providing that the diastereofacial selectivity of the organometal addition to the carbonyl was the same. Accordingly, *β*-**1** was treated with 2-trimethylsilylthiazole[48] (2-TST, **35**) (1.2 equiv) in CH_2Cl_2 at room temperature. Under these conditions a sluggish reaction took place. The almost complete consumption of *β*-**1** was reached after 50 h and treatment with two additional portions (1.2 equiv each) of 2-TST **35**. The resulting mixture of diastereomeric silylated alcohols[49] was oxidized by the Moffat reagent (Ac_2O−DMSO) to the ketone **36**, which was isolated in 72% yield from the aldehyde *β*-**1**. The addition of phenylmagnesium bromide to **36** in THF at −50 °C occurred with high selectivity too as the tertiary alcohol **37** was isolated as the sole product in almost quantitative yield.

The *R*- and *S*-configurations of the quaternary carbon atom of the alcohols **32** and **37**, both displaying the pyranose moiety in a $^2C_5$ conformation, were tentatively assigned by nOe difference experiments (400 MHz, $CDCl_3$). In the case of compound **32**, irradiation of the OH-1 proton led to a strong enhancement of the H-3 signal and a weak nOe with the H_{ortho} of the phenyl ring at C-1. Upon irradiation of these protons, a weak nOe with OH-1 and a strong enhancement of the H-2 signal were observed. We concluded that the tertiary alcohol **32** adopted a preferential conformation where the OH group was anti to H-2 and the compound was *R*-configured (Figure 3). Assuming the *S*-configuration for this compound one would expect the absence of nOe between OH-1 and the H_{ortho} of the phenyl ring. Similar NMR experiments carried out on compound **37** showed strong nOes between OH-1 and both H-2 and H-3. Moreover, irradiation of the H_{ortho} of the phenyl ring showed significant enhancements of the same H-2 and H-3

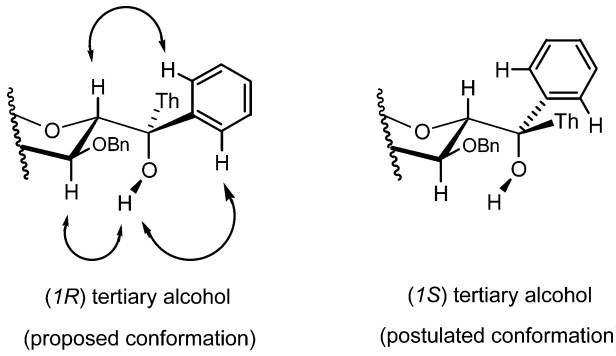


FIGURE 3. Nuclear Overhauser effects observed for the tertiary alcohol **32**.

signals. These effects indicated a free rotation around the *C*-glycosidic bond, thus excluding the possibility of any stereochemical assignment by this NMR technique. Hence, the *S*-configuration at C-1 in compound **37** was forcedly indirectly assigned as that of the epimer of the alcohol **32**.

Completion of the synthetic plan required only the transformation of the thiazole ring of compounds **32** and **37** into the carboxyl group. Guided by our extensive experience in this chemistry we were well aware of the need to proceed stepwise through aldehyde intermediates because no mild conditions were known to transform the thiazole ring directly into a carboxylate functionality.[50] Hence the thiazole-substituted alcohols **32** and **37** were first protected as *O*-benzyl ethers which in turn were subjected to the standard thiazole-to-formyl unmasking protocol.[51] The resulting aldehydes **33** and **38** were isolated in good to fair yields, i.e., 50% and 70%, respectively. Finally these aldehydes were considered for oxidation to carboxylic acids. This transformation was conveniently carried out with compound **33** by using the Jones' reagent. Esterification of the carboxylic group with

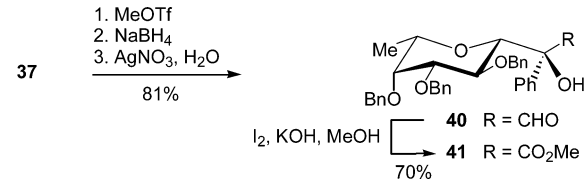
(48) Although 2-TST is commercially available, the high price leads to recommend its preparation on a multigram scale from inexpensive 2-bromothiazole. See: Dondoni, A.; Merino, P. *Org. Synth.* **1995**, *72*, 21.

(49) This material appeared to be a mixture of two diastereomeric silyl ethers in ca. 1:1 ratio (NMR analysis) slightly contaminated by the corresponding alcohols.

(50) The cleavage of the thiazole ring to amide via reaction with singlet oxygen has been reported in two instances (Matsuura, T.; Saito, I. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 2973. Wasylyk, J. M.; Biskupiak, J. E.; Costello, C. E.; Ireland, C. M. *J. Org. Chem.* **1983**, *48*, 4445). This method appears to be rather impractical and requires workup operations which are hardly compatible with the integrity of stereocenters and acid sensitive protective groups in the substrate.

(51) It is worth noting that in this case the reduction of the *N*-methyl thiazolium salt with $NaBH_4$ required heating in ethanol at 60 °C instead of the usual conditions (MeOH, 0 °C to room temperature).

SCHEME 9



diazomethane furnished the ester **34** in 72% yield. On the other hand, the aldehyde **38** turned out to be impervious to the treatment by usual oxidizing systems such as the Jones' reagent, TEMPO−BAIB, and I_2−KOH−MeOH. This may be ascribed to the heterogeneous conditions of these reactions since **38** was sparingly soluble in the relevant polar solvents. Moreover it is likely that this aldehyde is more encumbered than the isomer **33** and therefore less reactive. Deceptively, despite intense experimentation we were unable to find suitable conditions for the transformation of **38** to the ester **39**. This problem was overcome by using the hydroxy-free aldehyde **40** (Scheme 9) which, fortunately enough, displayed sufficient solubility in methanol. Noteworthy, this aldehyde was obtained in good yield from compound **37** by thiazole-to-formyl conversion despite the presence of the free hydroxy group, which in other systems was incompatible with this transformation.[52] Then, to our great delight, **40** was effectively oxidized to the methyl ester **41** simply by treatment with I_2 and KOH in 5:1 MeOH−CCl_4. This final transformation concluded successfully the synthetic plan.[53] Validation of this methodology by extension to the synthesis of other *C*-glycosyl phenylhydroxy acetates including the altrosyl derivatives (*R*)-**29** and (*S*)-**29** now appears of interest.

Conclusions

The ease of preparation of L-*C*-fucosyl aldehyde epimers α-**1** and *β*-**1** and their convenient use in synthetic approaches to three families of *C*-fucosides demonstrate once again the synthetic utility of anomeric sugar aldehydes as building blocks for complex *C*-glycosides without facing the task of controlling the anomeric configuration. Noteworthy is the new as well as highly stereoselective approach to *C*-glycosyl phenylhydroxy acetates as shown by the synthesis of the *C*-fucosyl derivatives (*R*)-**30** and (*S*)-**30**. However, the effectiveness and generality of this approach need to be demonstrated by the use of a significant number of *C*-glycosyl aldehydes. This issue is addressed by research underway in our laboratory. In addition to that, we foresee another possible route to the above sugar acetates via the Beau and Skrydstrup SmI_2-mediated coupling[54] of glycosylated pyridyl sulfones with phenyl thiazolyl ketone. However, crucial to the success of this approach is the full control of its stereochemical outcome to establish the required configuration at both the anomeric carbon of the sugar moiety and the newly formed quaternary carbon of the side chain.

Experimental Section

All moisture-sensitive reactions were performed under a nitrogen atmosphere in oven-dried glassware. Anhydrous solvents were dried over standard drying agents[55] and freshly distilled prior to use. Commercially available powdered 4 Å molecular sieves (5 μm average particle size) were used without further activation. Reactions were monitored by TLC on silica gel 60 F_{254} with detection by charring with sulfuric acid and/or ninhydrin. Flash column chromatography[56] was performed on silica gel 60 (230−400 mesh). Melting points were determined with a capillary apparatus. Optical rotations were measured at 20 ± 2 °C in the stated solvent; $[\alpha]_D$ values are given in deg·mL·g^{-1}·dm^{-1}. ^{1}H NMR spectra (300 and 400 MHz) were recorded for $CDCl_3$ solutions at room temperature unless otherwise specified; chemical shifts are in ppm (δ) from $SiMe_4$ (TMS) as internal standard; peak assignments were performed by ^{1}H−^{1}H COSY experiments. MALDI-TOF mass spectra were acquired with use of α-cyano-4-hydroxycinnamic acid as the matrix. Fuconolactone **3**[23] was prepared by oxidation of the corresponding hemiacetal **2**[24] with pyridinium chlorochromate.[57] The aldehyde **24** was synthesized by oxidation of the corresponding primary alcohol,[58] prepared as described.[59] 2-Trimethylsilylthiazole (2-TST, **31**), phenylmagnesium bromide, and 2-bromothiazole were commercially available. Alternatively, 2-TST **31** can be prepared as described.[48]

2,3,4-Tri-*O*-benzyl-1-*C*-(2-thiazolyl)-L-fucopyranose (5a). To a cooled (−78 °C), stirred solution of *n*BuLi (12.0 mL, 19.1 mmol, of a 1.6 M solution in hexane) in anhydrous Et_2O (25 mL) was added dropwise a solution of freshly distilled 2-bromothiazole (1.50 mL, 16.40 mmol) in anhydrous Et_2O (6.5 mL) over a 30-min period. The yellow solution was stirred at −75 °C for 30 min, then a solution of fuconolactone **3** (5.90 g, 13.64 mmol) in anhydrous Et_2O (25 mL) was added slowly (30 min). After an additional 30 min at −75 °C the mixture was allowed to warm to −65 °C in 30 min and then poured into 150 mL of a 1 M phosphate buffer at pH 7. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 150 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was eluted from a column of silica gel with cyclohexane−AcOEt (from 5:1 to 2:1) to give **5a** (6.56 g, 93%) as a syrup. $[\alpha]_D$ −6.5 (*c* 1.3, $CHCl_3$). ^{1}H NMR (300 MHz) δ 7.82 (d, 1 H, J = 3.2 Hz, Th), 7.48−7.19 and 7.08−7.04 (2 m, 16 H, 3 Ph, Th), 5.07 and 4.78 (2 d, 2 H, J = 12.0 Hz, PhCH_2), 4.80 (s, 2 H, PhCH_2), 4.70 and 4.31 (2 d, 2 H, J = 10.6 Hz, PhCH_2), 4.54 (s, 1 H, OH), 4.51 (d, 1 H, $J_{2,3}$ = 9.7 Hz, H-2), 4.26 (dq, 1 H, $J_{4,5}$ = 1.3 Hz, $J_{5,6}$ = 6.4 Hz, H-5), 4.04 (dd, 1 H, $J_{3,4}$ = 2.8 Hz, H-3), 3.77 (dd, 1 H, H-4), 1.26 (d, 3 H, 3 H-6). Anal. Calcd for $C_{30}H_{31}NO_5S$: C, 69.61; H, 6.04; N, 2.71. Found: C, 69.55; H, 5.82; N, 2.98.

1-*O*-Acetyl-2,3,4-tri-*O*-benzyl-1-*C*-(2-thiazolyl)-L-fucopyranose (5b). To a solution of **5a** (6.56 g, 12.68 mmol) in anhydrous CH_2Cl_2 (68 mL) were added at rt triethylamine (19 mL) and acetic anhydride (14 mL). The solution was kept at

(52) Dondoni, A.; Marra, A.; Perrone, D. *J. Org. Chem.* **1993**, *58*, 275.

(53) As requested by two reviewers, we have checked that compounds **34** and **41** are quantitatively hydrogenated under standard conditions (H_2, 1 bar, $Pd(OH)_2$, MeOH, rt, 1 h) to give *R*-**30** and *S*-**30**, respectively. Compound *R*-**30**: $[\alpha]_D$ −28.4 (*c* 0.2, MeOH). ^{1}H NMR (400 MHz, D_2O) δ 7.54−7.50 (m, 2 H, Ar), 7.28−7.18 (m, 3 H, Ar), 4.13 (d, 1 H, $J_{3,4}$ = 9.5 Hz, H-3), 3.67 (dd, 1 H, $J_{4,5}$ = 9.5 Hz, H-4), 3.66 (dq, 1 H, $J_{6,7}$ = 0.6 Hz, $J_{7,8}$ = 6.5 Hz, H-7), 3.61 (dd, 1 H, $J_{5,6}$ = 3.4 Hz, H-6), 3.58 (s, 3 H, OMe), 3.47 (dd, 1 H, H-5), 1.03 (d, 3 H, 3 H-8). Compound *S*-**30**: $[\alpha]_D$ −28.4 (*c* 0.6, MeOH). ^{1}H NMR (400 MHz, D_2O) δ 7.50−7.46 (m, 2 H, Ar), 7.31−7.26 (m, 2 H, Ar), 7.24−7.20 (m, 1 H, Ar), 4.22 (d, 1 H, $J_{3,4}$ = 9.6 Hz, H-3), 3.80 (dd, 1 H, $J_{4,5}$ = 9.2 Hz, H-4), 3.64 (dq, 1 H, $J_{6,7}$ = 0.8 Hz, $J_{7,8}$ = 6.4 Hz, H-7), 3.61 (dd, 1 H, $J_{5,6}$ = 3.6 Hz, H-6), 3.59 (dd, 1 H, H-5), 3.46 (s, 3 H, OMe), 0.86 (d, 3 H, 3 H-8).

(54) Skrydstrup, T.; Jarreton, O.; Mazéas, D.; Urban, D.; Beau, J.-M. *Chem. Eur. J.* **1998**, *4*, 655.

(55) Armarego, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals*, 4th ed.; Butterworth-Heinemann: Oxford, UK, 1996.

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rt for 42 h and then concentrated. Crystallization of the crude product from hot cyclohexane gave pure **5b** (3.00 g, 42%) as white crystals. The mother liquor was concentrated and the residue was eluted from a column of silica gel with cyclohexane−AcOEt (from 3:1 to 1:1) to give **5b** (3.59 g, 51%) as a white solid. Mp 125−126 °C (cyclohexane); $[\alpha]_D$ −41.5 (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz) δ 7.80 (d, 1 H, J = 3.2 Hz, Th), 7.40−7.25 (m, 16 H, 3 Ph, Th), 5.05 and 4.75 (2 d, 2 H, J = 11.8 Hz, PhCH_2), 4.86 and 4.78 (2 d, 2 H, J = 11.8 Hz, PhCH_2), 4.51 and 4.25 (2 d, 2 H, J = 10.7 Hz, PhCH_2), 4.13 (dd, 1 H, $J_{2,3}$ = 10.0 Hz, $J_{3,4}$ = 2.3 Hz, H-3), 4.09 (d, 1 H, H-2), 3.98 (dq, 1 H, $J_{4,5}$ = 1.3 Hz, $J_{5,6}$ = 6.5 Hz, H-5), 3.89 (dd, 1 H, H-4), 2.19 (s, 3 H, Ac), 1.32 (d, 3 H, 3 H-6). Anal. Calcd for $C_{32}H_{33}NO_6S$: C, 68.67; H, 5.94; N, 2.50. Found: C, 68.77; H, 5.70; N, 2.65.

When the crude thiazolylketose **5a** derived from lactone **3** (9.80 g) was directly acetylated as described above, the compound **5b** was isolated by column chromatography in 92% overall yield from **1**.

2-(2,3,4-Tri-*O*-benzyl-β-L-fucopyranosyl)thiazole (6). To a stirred mixture of **5b** (1.60 g, 2.86 mmol), activated 4-Å powdered molecular sieves (2.8 g), and triethylsilane (4.61 mL, 28.60 mmol) in anhydrous CH_2Cl_2 (47 mL) was added TMSOTf (776 μL, 4.29 mmol). The mixture was stirred at rt for 1 h, then diluted with triethylamine (2.5 mL) and CH_2Cl_2 (50 mL), filtered through Celite, and concentrated. The residue was eluted from a column of silica gel with cyclohexane−AcOEt (from 3:1 to 1:1) to give **6** (1.37 g, 95%) as a white solid. Mp 113−114 °C (cyclohexane); $[\alpha]_D$ +6.3 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz) δ 7.84 (d, 1 H, J = 3.3 Hz, Th), 7.48−7.20 and 7.12−7.06 (2 m, 16 H, 3 Ph, Th), 5.08 and 4.77 (2 d, 2 H, J = 11.7 Hz, PhCH_2), 4.81 (s, 2 H, PhCH_2), 4.69 and 4.31 (2 d, 2 H, J = 10.7 Hz, PhCH_2), 4.68 (d, 1 H, $J_{1,2}$ = 9.5 Hz, H-1), 4.24 (dd, 1 H, $J_{2,3}$ = 9.0 Hz, H-2), 3.76 (dd, 1 H, $J_{3,4}$ = 2.7 Hz, H-3), 3.75−3.68 (m, 2 H, H-4, H-5), 1.27 (d, 3 H, $J_{5,6}$ = 6.3 Hz, 3 H-6). Anal. Calcd for $C_{30}H_{31}NO_4S$: C, 71.83; H, 6.23; N, 2.79. Found: C, 72.02; H, 6.10; N, 2.95.

Preparation of the SmI_2 Solution. To a stirred mixture of commercially available samarium (1.65 g, 11.0 mmol, <40 mesh powder) and I_2 (2.55 g, 10.0 mmol) in a septum-equipped vial was added anhydrous THF (100 mL) under a nitrogen atmosphere. An exothermic reaction took place and the solution turned brownish while large amounts of SmI_3 were formed as a yellow solid after ca. 15 min. The septum was replaced by a gastight screw-cap and the mixture was stirred at 75 °C for an additional 3 h. Upon stirring at high temperature the yellow precipitate dissolved and the suspension turned deep blue due to the formation of SmI_2. The ca. 0.1 M samarium(II) iodide solution was stored at rt and used within 1 day.

2-(2,3,4-Tri-*O*-benzyl-α-L-fucopyranosyl)thiazole (7). A vigorously stirred solution of **5b** (1.08 g, 1.93 mmol) and anhydrous ethylene glycol (1.20 g, 19.30 mmol) in anhydrous THF (10 mL) was degassed under vacuum and saturated with argon three times, then a ca. 0.1 M solution of SmI_2 in THF was added dropwise by means of a gastight syringe until the reaction mixture turned a persistent blue (usually after 10−20 min). The mixture was stirred for an additional 10 min, then diluted with saturated aqueous $NaHCO_3$ (100 mL) and concentrated to remove the THF. The residue was extracted with Et_2O (2 × 100 mL), and the combined organic phases were dried (Na_2SO_4) and concentrated. The residue was eluted from a column of silica gel with cyclohexane−AcOEt (from 4:1 to 1:1) to give first **7** (0.90 g, 93%) as a syrup. $[\alpha]_D$ −40.5 (*c* 1.3, $CHCl_3$); ^{1}H NMR (400 MHz) δ 7.78 (d, 1 H, J = 3.3 Hz, Th), 7.36−7.23 and 7.11−7.06 (2 m, 16 H, 3 Ph, Th), 5.40 (d, 1 H, $J_{1,2}$ = 3.3 Hz, H-1), 4.69 (s, 2 H, PhCH_2), 4.67 and 4.58 (2 d, 2 H, J = 12.0 Hz, PhCH_2), 4.39 and 4.36 (2 d, 2 H, J = 11.5 Hz, PhCH_2), 4.34 (dq, 1 H, $J_{4,5}$ = 4.6 Hz, $J_{5,6}$ = 6.5 Hz, H-5), 4.19 (dd, 1 H, $J_{2,3}$ = 5.7 Hz, H-2), 3.99 (dd, 1 H, $J_{3,4}$ = 3.1 Hz, H-3), 3.95 (dd, 1 H, H-4), 1.42 (d, 3 H, 3 H-6). Anal. Calcd for $C_{30}H_{31}NO_4S$: C, 71.83; H, 6.23; N, 2.79. Found: C, 71.45; H, 6.01; N, 2.82. Eluted second was **6** (64 mg, 6%).

2,6-Anhydro-3,4,5-tri-*O*-benzyl-7-deoxy-*aldehydo*-L-*glycero*-D-*gluco*-heptose (α-1). A mixture of **7** (960 mg, 1.91 mmol), activated 4-Å powdered molecular sieves (2.0 g), and anhydrous CH_3CN (19 mL) was stirred at rt for 10 min, then methyl triflate (280 μL, 2.48 mmol) was added. The suspension was stirred at rt for 15 min and then concentrated to dryness without filtering off the molecular sieves. To a cooled (0 °C), stirred suspension of the crude *N*-methylthiazolium salt in CH_3OH (19 mL) was added $NaBH_4$ (146 mg, 3.82 mmol). The mixture was stirred at rt for an additional 10 min, diluted with acetone, filtered through a pad of Celite, and concentrated. To a vigorously stirred solution of the thiazolidines in CH_3CN (20 mL) was added dropwise H_2O (2 mL) and then $AgNO_3$ in one portion (486 mg, 2.86 mmol). The mixture was stirred at rt for 10 min, then diluted with 1 M phosphate buffer at pH 7 (40 mL) and partially concentrated to remove CH_3CN (bath temperature not exceeding 40 °C). The suspension was extracted with CH_2Cl_2 (100 + 50 mL), and the combined organic phases were dried (Na_2SO_4) and concentrated to give a yellow syrup. A solution of the residue in Et_2O (ca. 150 mL) was filtered through a pad of Celite (1 × 4 cm, h × d), and concentrated to afford α-**1** (770 mg, 90%) as a colorless syrup ca. 95% pure by ^{1}H NMR analysis. ^{1}H NMR (400 MHz) δ 9.79 (s, 1 H, H-1), 7.39−7.23 (m, 15 H, 3 Ph), 4.73 and 4.65 (2 d, 2 H, J = 11.8 Hz, PhCH_2), 4.72 and 4.59 (2 d, 2 H, J = 12.0 Hz, PhCH_2), 4.67 and 4.59 (2 d, 2 H, J = 11.8 Hz, PhCH_2), 4.42 (d, 1 H, $J_{2,3}$ = 4.6 Hz, H-2), 4.21 (dd, 1 H, $J_{3,4}$ = 7.0 Hz, H-3), 4.18 (dq, 1 H, $J_{5,6}$ = 3.7 Hz, $J_{6,7}$ = 6.5 Hz, H-6), 3.80 (dd, 1 H, $J_{4,5}$ = 2.8 Hz, H-5), 3.67 (dd, 1 H, H-4), 1.32 (d, 3 H, 3 H-7).

2,6-Anhydro-3,4,5-tri-*O*-benzyl-7-deoxy-*aldehydo*-L-*glycero*-D-*manno*-heptose (β-1). The thiazolyl *C*-glycoside **6** (260 mg, 0.51 mmol) was treated as described for the preparation of α-**1** to give β-**1** (213 mg, 92%) as a colorless syrup ca. 95% pure by ^{1}H NMR analysis. ^{1}H NMR (400 MHz) δ 9.65 (d, 1 H, $J_{1,2}$ = 1.5 Hz, H-1), 7.40−7.28 (m, 15 H, 3 Ph), 4.99 and 4.70 (2 d, 2 H, J = 11.6 Hz, PhCH_2), 4.88 and 4.68 (2 d, 2 H, J = 10.7 Hz, PhCH_2), 4.78 and 4.75 (2 d, 2 H, J = 11.5 Hz, PhCH_2), 4.06 (dd, 1 H, $J_{2,3}$ = 10.1 Hz, $J_{3,4}$ = 8.4 Hz, H-3), 3.73 (dd, 1 H, H-2), 3.69−3.65 (m, 2 H, H-4, H-5), 3.56 (dq, 1 H, $J_{5,6}$ = 0.8 Hz, $J_{6,7}$ = 6.4 Hz, H-6), 1.22 (d, 3 H, 3 H-7).

(*Z*)-8,12-Anhydro-9,10,11-tri-*O*-benzyl-6,7,13-trideoxy-1,2:3,4-di-*O*-isopropylidene-α-L-*glycero*-D-*manno*-D-*galacto*-tridec-6-eno-1,5-pyranose (9). A mixture of phosphonium salt **8** (280 mg, 0.44 mmol), activated 4-Å powdered molecular sieves (0.40 g), anhydrous THF (2.3 mL), and anhydrous HMPA (1.1 mL) was stirred at room temperature for 10 min, then cooled to −30 °C. To the stirred mixture was added dropwise *n*-butyllithium (275 μL, 0.44 mmol of a 1.6 M solution in hexanes) and, after 5 min, a solution of β-**1** (182 mg, 0.40 mmol) in anhydrous THF (1 mL) over a 10-min period. The mixture was stirred at −30 °C for an additional 30 min, then allowed to reach −10 °C in 1.5 h, diluted with Et_2O (100 mL), and filtered through a pad of Celite. The ethereal solution was washed with 1 M phosphate buffer at pH 7 (3 × 10 mL), dried (Na_2SO_4), and concentrated. Column chromatography (5:1 cyclohexane−AcOEt containing 0.2% of Et_3N) of the residue afforded **9** (157 mg, 57%) as a syrup. $[\alpha]_D$ −49.8 (*c* 1.4, $CHCl_3$); ^{1}H NMR (400 MHz) δ 7.39−7.24 (m, 15 H, 3 Ph), 5.75 (ddd, 1 H, $J_{5,6}$ = 6.9 Hz, $J_{6,7}$ = 11.5 Hz, $J_{6,8}$ = 1.0 Hz, H-6), 5.69 (dd, 1 H, $J_{7,8}$ = 5.1 Hz, H-7), 5.54 (d, 1 H, $J_{1,2}$ = 5.0 Hz, H-1), 4.99 and 4.69 (2 d, 2 H, J = 11.7 Hz, PhCH_2), 4.86 and 4.75 (2 d, 2 H, J = 11.3 Hz, PhCH_2), 4.80 (dd, 1 H, $J_{4,5}$ = 1.7 Hz, H-5), 4.74 and 4.71 (2 d, 2 H, J = 11.9 Hz, PhCH_2), 4.51 (dd, 1 H, $J_{2,3}$ = 2.3 Hz, $J_{3,4}$ = 7.8 Hz, H-3), 4.36 (dd, 1 H, H-4), 4.27 (dd, 1 H, H-2), 3.92 (ddd, 1 H, $J_{8,9}$ = 9.5 Hz, H-8), 3.81 (dd, 1 H, $J_{9,10}$ = 9.2 Hz, H-9), 3.64 (dd, 1 H, $J_{10,11}$ = 2.7 Hz, $J_{11,12}$ = 0.9 Hz, H-11), 3.56 (dd, 1 H, H-10), 3.48 (dq, 1 H, $J_{12,13}$ = 6.4 Hz, H-12), 1.50, 1.46, 1.32, and 1.25 (4 s, 12 H, 4 Me), 1.17 (d, 3 H, 3 H-13). Anal. Calcd for $C_{40}H_{48}O_9$: C, 71.41; H, 7.19. Found: C, 71.13; H, 7.01.

9,10,11-Tri-*O*-acetyl-8,12-anhydro-6,7,13-trideoxy-1,2:3,4-di-*O*-isopropylidene-α-L-*glycero*-D-*manno*-D-*galacto*-

trideco-1,5-pyranose (10). A vigorously stirred mixture of **9** (90 mg, 0.13 mmol), 20% palladium hydroxide on carbon (31 mg), and 1:1 CH_3OH−AcOEt (4 mL) was degassed under vacuum and saturated with hydrogen (by a H_2-filled balloon) three times. The suspension was stirred at rt for 3 h under a slightly positive pressure of hydrogen (balloon), then filtered through a plug of cotton and concentrated. A solution of the crude triol in pyridine (2 mL) and acetic anhydride (2 mL) was kept at rt for 20 h, then concentrated. The residue was eluted from a column of silica gel with cyclohexane−AcOEt (from 3:1 to 1:1) to give **10** (60 mg, 84%) as a syrup. $[\alpha]_D$ −41.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz) δ 5.53 (d, 1 H, $J_{1,2}$ = 5.1 Hz, H-1), 5.27 (dd, 1 H, $J_{10,11}$ = 3.3 Hz, $J_{11,12}$ = 1.2 Hz, H-11), 5.09 (dd, 1 H, $J_{8,9}$ = 9.4 Hz, $J_{9,10}$ = 10.0 Hz, H-9), 5.00 (dd, 1 H, H-10), 4.60 (dd, 1 H, $J_{2,3}$ = 2.3 Hz, $J_{3,4}$ = 8.0 Hz, H-3), 4.30 (dd, 1 H, H-2), 4.15 (dd, 1 H, $J_{4,5}$ = 1.8 Hz, H-4), 3.77−3.69 (m, 1 H, H-5), 3.73 (dq, 1 H, $J_{12,13}$ = 6.5 Hz, H-12), 3.44−3.37 (m, 1 H, H-8), 2.19, 2.06, and 1.99 (3 s, 9 H, 3 Ac), 1.68−1.62 (m, 4 H, 2 H-6, 2 H-7), 1.53, 1.47, 1.36, and 1.34 (4 s, 12 H, 4 Me), 1.17 (d, 3 H, 3 H-13). Anal. Calcd for $C_{25}H_{38}O_{12}$: C, 56.59; H, 7.22. Found: C, 56.32; H, 7.11.

(*Z*,*E*)-8,12-Anhydro-9,10,11-tri-*O*-benzyl-6,7,13-trideoxy-1,2:3,4-di-*O*-isopropylidene-α-L-*glycero*-D-*gluco*-D-*galacto*-tridec-6-eno-1,5-pyranose (12). The aldehyde α-**1** (270 mg, 0.60 mmol) was allowed to react with the phosphonium salt **8** (419 mg, 0.67 mmol) in the presence of BuLi (425 μL, 0.68 mmol of a 1.6 M solution in hexanes) as described for the preparation of **9**. The crude product was eluted from a column of silica gel with 4:1 cyclohexane−AcOEt (containing 0.3% of Et_3N) to give first syrupy **12** (194 mg, 48%) as a ca. 4:1 *Z*,*E* mixture. (*Z*)-**12**: ^{1}H NMR (400 MHz) (selected data) δ 5.94 (dd, 1 H, $J_{6,7}$ = 11.5 Hz, $J_{7,8}$ = 6.5 Hz, H-7), 5.84 (ddd, 1 H, $J_{5,6}$ = 7.9 Hz, $J_{6,8}$ = 0.8 Hz, H-6), 5.53 (d, 1 H, $J_{1,2}$ = 5.3 Hz, H-1). (*E*)-**12**: ^{1}H NMR (400 MHz) δ 7.40−7.25 (m, 15 H, 3 Ph), 6.04 (dd, 1 H, $J_{6,7}$ = 16.1 Hz, $J_{7,8}$ = 4.0 Hz, H-7), 5.97 (ddd, 1 H, $J_{5,6}$ = 5.8 Hz, $J_{6,8}$ = 1.4 Hz, H-6), 5.61 (d, 1 H, $J_{1,2}$ = 5.0 Hz, H-1), 4.85 and 4.65 (2 d, 2 H, *J* = 11.8 Hz, PhCH_2), 4.74 (s, 2 H, PhCH_2), 4.67 (ddd, 1 H, $J_{8,9}$ = 4.8 Hz, H-8), 4.65 (s, 2 H, PhCH_2), 4.62 (dd, 1 H, $J_{2,3}$ = 2.4 Hz, $J_{3,4}$ = 7.8 Hz, H-3), 4.36 (dd, 1 H, $J_{4,5}$ = 2.0 Hz, H-5), 4.35 (dd, 1 H, H-2), 4.22 (dd, 1 H, H-4), 4.04 (dd, 1 H, $J_{9,10}$ = 8.1 Hz, H-9), 4.02 (dq, 1 H, $J_{11,12}$ = 2.6 Hz, $J_{12,13}$ = 6,5 Hz, H-12), 3.76 (dd, 1 H, $J_{10,11}$ = 2.8 Hz, H-11), 3.72 (dd, 1 H, H-10), 1.55, 1.44, 1.36, and 1.33 (4 s, 12 H, 4 Me), 1.24 (s, 3 H, 3 H-13). Anal. Calcd for $C_{40}H_{48}O_9$: C, 71.41; H, 7.19. Found: C, 71.28; H, 7.13.

Eluted second was **13** (20 mg, 8%) slightly contaminated by uncharacterized byproducts. ^{1}H NMR (300 MHz) δ 9.20 (s, 1 H, H-1), 7.42−7.26 (m, 10 H, 2 Ph), 5.85 (dd, 1 H, $J_{3,4}$ = 2.4 Hz, $J_{3,5}$ = 1.8 Hz, H-3), 5.00 and 4.76 (2 d, 2 H, *J* = 11.8 Hz, PhCH_2), 4.77 and 4.73 (2 d, 2 H, *J* = 12.0 Hz, PhCH_2), 4.47 (ddd, 1 H, $J_{4,5}$ = 4.1 Hz, $J_{4,6}$ = 1.3 Hz, H-4), 4.17 (ddq, 1 H, $J_{5,6}$ = 1.5 Hz, $J_{6,7}$ = 6.7 Hz, H-6), 3.78 (ddd, 1 H, H-5), 1.40 (d, 3 H, 3 H-7).

Methyl 8,12-Anhydro-2,3,4,9,10,11-hexa-*O*-benzyl-6,7,-13-trideoxy-α-L-*glycero*-D-*gluco*-D-*gluco*-tridec-6-(*Z*,*E*)-eno-1,5-pyranoside (14). The aldehyde α-**1** (200 mg, 0.44 mmol) was allowed to react with the phosphonium salt **11** (370 mg, 0.44 mmol) in the presence of BuLi (275 μL, 0.44 mmol of a 1.6 M solution in hexanes) as described for the preparation of **9**. The crude product was eluted from a column of silica gel with cyclohexane−AcOEt (from 7:1 to 4:1) to give **14** (144 mg, 37%) as a 1:1 mixture of *E*,*Z*-isomers. ^{1}H NMR (300 MHz) (selected data) δ 6.15 (dd, 1 H, $J_{6,7}$ = 16.0 Hz, $J_{7,8}$ = 4.4 Hz, H-7*E*), 6.05 (dd, 1 H, $J_{6,7}$ = 11.2 Hz, $J_{7,8}$ = 6.8 Hz, H-7*Z*), 5.91 (ddd, 1 H, $J_{5,6}$ = 6.7 Hz, $J_{6,8}$ = 1.8 Hz, H-6*E*), 5.69 (ddd, 1 H, $J_{5,6}$ = 9.0 Hz, $J_{6,8}$ = 1.2 Hz, H-6*Z*), 3.41 (s, 3 H, OMe), 3.40 (s, 3 H, OMe), 1.24 (d, 3 H, $J_{12,13}$ = 6.5 Hz, 3 H-13), 1.10 (d, 3 H, $J_{12,13}$ = 6.5 Hz, 3 H-13). Anal. Calcd for $C_{56}H_{60}O_9$: C, 76.69; H, 6.90. Found: C, 76.38; H, 6.77.

9,10,11-Tri-*O*-acetyl-8,12-anhydro-6,7,13-trideoxy-1,2:3,4-di-*O*-isopropylidene-α-L-*glycero*-D-*gluco*-D-*galacto*-trideco-1,5-pyranose (15). The alkene **12** (197 mg, 0.29 mmol) was hydrogenated and acetylated as described for the preparation of **10** to give, after column chromatography on silica gel (2:1 cyclohexane−AcOEt), **15** (121 mg, 80%) as a syrup. $[\alpha]_D$ −97.7 (*c* 0.9, $CHCl_3$); ^{1}H NMR (300 MHz) δ 5.55 (d, 1 H, $J_{1,2}$ = 5.1 Hz, H-1), 5.35 (dd, 1 H, $J_{8,9}$ = 5.8 Hz, $J_{9,10}$ = 10.2 Hz, H-9), 5.29 (dd, 1 H, $J_{10,11}$ = 3.3 Hz, $J_{11,12}$ = 1.7 Hz, H-11), 5.22 (dd, 1 H, H-10), 4.62 (dd, 1 H, $J_{2,3}$ = 2.3 Hz, $J_{3,4}$ = 8.0 Hz, H-3), 4.33 (dd, 1 H, H-2), 4.22−4.16 (m, 1 H, H-8), 4.16 (dd, 1 H, $J_{4,5}$ = 1.7 Hz, H-4), 3.96 (dq, 1 H, $J_{12,13}$ = 6.4 Hz, H-12), 3.76−3.71 (m, 1 H, H-5), 2.18, 2.08, and 2.02 (3 s, 9 H, 3 Ac), 1.76−1.65 (m, 4 H, 2 H-6, 2 H-7), 1.56, 1.48, 1.37, and 1.36 (4 s, 12 H, 4 Me), 1.16 (d, 3 H, 3 H-13). Anal. Calcd for $C_{25}H_{38}O_{12}$: C, 56.59; H, 7.22. Found: C, 56.37; H, 7.00.

Methyl 2,3,4,9,10,11-Hexa-*O*-acetyl-8,12-anhydro-6,7,-13-trideoxy-α-L-*glycero*-D-*gluco*-D-*gluco*-trideco-1,5-pyranoside (16). The alkene **14** (144 mg, 0.16 mmol) was hydrogenated and acetylated as described for the preparation of **10** to give, after column chromatography on silica gel (1:1 cyclohexane−AcOEt), **16** (58 mg, 60%) as a syrup. $[\alpha]_D$ +31.3 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6) δ 5.84 (dd, 1 H, $J_{2,3}$ = 10.3 Hz, $J_{3,4}$ = 9.4 Hz, H-3), 5.68 (dd, 1 H, $J_{8,9}$ = 5.7 Hz, $J_{9,10}$ = 10.3 Hz, H-9), 5.43 (dd, 1 H, $J_{10,11}$ = 3.5 Hz, H-10), 5.36 (dd, 1 H, $J_{11,12}$ = 1.7 Hz, H-11), 5.08 (dd, 1 H, $J_{4,5}$ = 10.0 Hz, H-4), 5.00 (dd, 1 H, $J_{1,2}$ = 3.7 Hz, H-2), 4.86 (d, 1 H, H-1), 4.26 (ddd, 1 H, $J_{7a,8}$ = 4.0 Hz, $J_{7b,8}$ = 10.4 Hz, H-8), 3.71 (ddd, 1 H, $J_{5,6a}$ = 2.8 Hz, $J_{5,6b}$ = 7.4 Hz, H-5), 3.38 (dq, 1 H, $J_{12,13}$ = 6.5 Hz, H-12), 2.96 (s, 3 H, OMe), 1.72, 1.71, 1.70, 1.64, 1.62, and 1.60 (6 s, 18 H, 6 Ac), 1.72−1.65 and 1.35−1.30 (2 m, 4 H, 2 H-6, 2 H-7), 0.95 (d, 3 H, 3 H-13). Anal. Calcd for $C_{26}H_{38}O_{15}$: C, 52.88; H, 6.49. Found: C, 52.50; H, 6.39.

2,6-Anhydro-3,4,5-tri-*O*-benzyl-7-deoxy-L-*glycero*-D-*gluco*-heptitol (17). (a) To a cooled (0 °C), stirred solution of aldehyde α-**1** (730 mg, 1.63 mmol) in Et_2O (9 mL) and CH_3OH (9 mL) was added $NaBH_4$ (120 mg, 3.26 mmol). The mixture was stirred at rt for an additional 10 min, then diluted with acetone (1 mL), and concentrated. The residue was eluted from a column of silica gel with 2:1 cyclohexane−AcOEt to give **17** (696 mg, 95%) as a syrup. $[\alpha]_D$ −12.6 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz) δ 7.36−7.24 (m, 15 H, 3 Ph), 4.77 and 4.67 (2 d, 2 H, *J* = 12.0 Hz, PhCH_2), 4.76 and 4.62 (2 d, 2 H, *J* = 11.8 Hz, PhCH_2), 4.65 and 4.51 (2 d, 2 H, *J* = 11.7 Hz, PhCH_2), 4.12 (ddd, 1 H, $J_{1a,2}$ = 7.8 Hz, $J_{1b,2}$ = 4.8 Hz, $J_{2,3}$ = 3.9 Hz, H-2), 4.00 (dq, 1 H, $J_{5,6}$ = 3.5 Hz, $J_{6,7}$ = 6.7 Hz, H-6), 3.92−3.88 (m, 1 H, H-3), 3.81 (ddd, 1 H, $J_{1a,1b}$ = 11.6 Hz, $J_{1a,OH}$ = 3.6 Hz, H-1a), 3.81−3.78 (m, 2 H, H-4, H-5), 3.69 (ddd, 1 H, $J_{1b,OH}$ = 8.7 Hz, H-1b), 1.97 (dd, 1 H, OH), 1.30 (d, 3 H, 3 H-7). Anal. Calcd for $C_{28}H_{32}O_5$: C, 74.97; H, 7.19. Found: C, 74.81; H, 7.15.

(b) A mixture of **7** (1.60 g, 3.58 mmol), activated 4 Å powdered molecular sieves (3.0 g), and anhydrous CH_3CN (35 mL) was stirred at rt for 10 min, then methyl triflate (610 μL, 5.37 mmol) was added. The suspension was stirred at rt for 15 min and then concentrated to dryness without filtering off the molecular sieves. To a cooled (0 °C), stirred suspension of the crude *N*-methylthiazolium salt in CH_3OH (35 mL) was added $NaBH_4$ (331 mg, 8.95 mmol). The mixture was stirred at rt for an additional 10 min, diluted with acetone, filtered through a pad of Celite, and concentrated. To a vigorously stirred solution of the thiazolidines in CH_3CN (30 mL) was added dropwise H_2O (3 mL) and then $AgNO_3$ in one portion (912 mg, 5.37 mmol). The mixture was stirred at rt for 10 min, then $NaBH_4$ (397 mg, 10.74 mmol) was added. Stirring was continued for an additional 15 min, then the reaction mixture was diluted with acetone, filtered through a pad of Celite, and concentrated. The residue was eluted from a column of silica gel with 2:1 cyclohexane−AcOEt to give **17** (1.56 g, 97%).

2,6-Anhydro-3,4,5-tri-*O*-benzyl-1,7-dideoxy-1-iodo-L-*glycero*-D-*gluco*-heptitol (18). To a vigorously stirred solution of alcohol **17** (760 mg, 1.69 mmol), triphenylphosphine (1.11 g, 4.23 mmol), and imidazole (575 mg, 8.45 mmol) in anhydrous toluene (17 mL) was added iodine (1.07 g, 4.22 mmol). The mixture was stirred at 80 °C for 1 h, then cooled

to rt, filtered through a pad of Celite, and concentrated. A solution of the residue in Et_2O (200 mL) was washed with 5% aqueous $Na_2S_2O_3$ (2 × 50 mL), dried (Na_2SO_4), and concentrated. The residue was eluted from a column of silica gel with 11:1 cyclohexane−AcOEt to give **18** (880 mg, 93%) as a white solid. Mp 74−75 °C (MeOH); $[\alpha]_D$ −20.3 (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz) δ 7.37−7.24 (m, 15 H, 3 Ph), 4.74 and 4.63 (2 d, 2 H, J = 12.0 Hz, PhCH_2), 4.71 and 4.59 (2 d, 2 H, J = 11.9 Hz, PhCH_2), 4.62 and 4.53 (2 d, 2 H, J = 11.8 Hz, PhCH_2), 4.15 (ddd, 1 H, $J_{1a,2}$ = 5.7 Hz, $J_{1b,2}$ = 8.9 Hz, $J_{2,3}$ = 3.5 Hz, H-2), 3.94 (dd, 1 H, $J_{3,4}$ = 6.5 Hz, H-3), 3.79 (dd, 1 H, $J_{4,5}$ = 3.0 Hz, H-5), 3.74 (dd, 1 H, H-4), 3.34 (dd, 1 H, $J_{1a,1b}$ = 10.4 Hz, H-1a), 3.27 (dd, 1 H, H-1b), 1.34 (d, 3 H, 3 H-7). Anal. Calcd for $C_{28}H_{31}IO_4$: C, 60.22; H, 5.60. Found: C, 60.24; H, 5.35.

(2,6-Anhydro-3,4,5-tri-*O*-benzyl-1,7-dideoxy-L-*glycero*-D-*gluco*-heptitol-1-yl)triphenylphosphonium Iodide (19). A mixture of iodide **18** (830 mg, 1.48 mmol) and triphenylphosphine (2.20 g, 8.45 mmol) was stirred at 120 °C under a nitrogen atmosphere for 2 h, then cooled to ca. 80 °C, diluted with toluene (1 mL), transferred onto a column of silica gel, and eluted with toluene, then AcOEt, and finally 1:1 AcOEt−acetone to give **19** (1.18 g, 97%) as a foam. $[\alpha]_D$ −34.7 (*c* 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, acetone-d_6) δ 7.98−7.86, 7.79−7.73, and 7.41−7.26 (3 m, 30 H, 6 Ph), 4.80 (s, 2 H, PhCH_2), 4.79 and 4.67 (2 d, 2 H, J = 11.9 Hz, PhCH_2), 4.73 and 4.54 (2 d, 2 H, J = 11.6 Hz, PhCH_2), 4.44 (ddd, 1 H, $J_{1a,1b}$ = 15.3 Hz, $J_{1a,2}$ = 11.0 Hz, $J_{1a,P}$ = 21.7 Hz, H-1a), 4.43−4.36 (m, 2 H, H-2, H-4), 4.11−4.04 (m, 2 H, H-3, H-6), 3.92 (dd, 1 H, $J_{4,5}$ = 3.0 Hz, $J_{5,6}$ = 3.9 Hz, H-5), 3.60 (ddd, 1 H, $J_{1b,2}$ = 2.0 Hz, $J_{1b,P}$ = 15.5 Hz, H-1b), 0.60 (d, 3 H, $J_{6,7}$ = 6.5 Hz, H-7); ^{31}P NMR (162 MHz, acetone-d_6) δ 26.3. Anal. Calcd for $C_{46}H_{46}IO_4P$: C, 67.32; H, 5.65. Found: C, 67.55; H, 5.46.

5,9-Anhydro-6,7,8-tri-*O*-benzyl-2-*tert*-butoxycarbonylamino-2,3,4,10-tetradeoxy-1,2-*N*,*O*-isopropylidene-L-*threo*-D-*gulo*- and -D-*ido*-dec-3-(*Z*,*E*)-enitol (21). A mixture of phosphonium salt **19** (195 mg, 0.24 mmol), activated 4-Å powdered molecular sieves (0.24 g), anhydrous THF (1.6 mL), and anhydrous HMPA (1.6 mL) was stirred at room temperature for 10 min, then cooled to −20 °C. The stirred mixture was treated with *n*-butyllithium (180 μL, 0.28 mmol of a 1.6 M solution in hexanes), warmed to 0 °C, stirred for an additional 30 min, and then cooled to −20 °C. To the stirred mixture was added a solution of **20** (92 mg, 0.40 mmol) in anhydrous THF (1.6 mL) over a 10-min period. The mixture was allowed to reach 0 °C in 2.5 h, stirred at 0 °C for an additional 60 min, then diluted with Et_2O (150 mL), and filtered through a pad of Celite. The ethereal solution was washed with 1 M phosphate buffer at pH 7 (3 × 30 mL), dried (Na_2SO_4), and concentrated. The residue was eluted from a column of silica gel with cyclohexane−AcOEt (from 8:1 to 4:1, containing 0.3% of Et_3N) to give syrupy **21** (106 mg, 70%) as a 3:1 *E*,*Z* mixture. ^{1}H NMR (300 MHz, DMSO-d_6, 120 °C) (selected data) δ 5.86 (dd, 1 H, J = 4.4, 15.9 Hz, CH═), 5.83 (dd, J = 6.1, 11.0 Hz, CH═), 5.77 (ddd, J = 0.8, 5.8, 15.9 Hz, CH═), 5.71 (ddd, J = 1.5, 5.0, 11.0 Hz, CH═), 5.56 (ddd, J = 1.5, 8.2, 11.3 Hz, CH═), 1.21 (d, $J_{9,10}$ = 6.3 Hz, H-10), 1.18 (d, $J_{9,10}$ = 6.3 Hz, H-10), 1.16 (d, $J_{9,10}$ = 6.3 Hz, H-10); MALDI-TOF MS (643.83) 665.6 (M^+ + Na), 681.7 (M^+ + K). Anal. Calcd for $C_{39}H_{49}NO_7$: C, 72.76; H, 7.67; N, 2.18. Found: C, 72.58; H, 7.52; N, 2.31.

6,7,8-Tri-*O*-acetyl-5,9-anhydro-2-*tert*-butoxycarbonylamino-2,3,4,10-tetradeoxy-1,2-*N*,*O*-isopropylidene-L-*threo*-D-*gulo*- and -D-*ido*-decitol (22). A vigorously stirred mixture of **21** (90 mg, 0.14 mmol), 20% palladium hydroxide on carbon (31 mg), and 1:1 CH_3OH−AcOEt (4 mL) was degassed under vacuum and saturated with hydrogen (by a H_2-filled balloon) three times. The suspension was stirred at rt for 1 h under a positive pressure of hydrogen (5 bar), then filtered through a plug of cotton and concentrated. A solution of the crude triol in pyridine (1 mL) and freshly distilled acetic anhydride (1 mL) was kept at rt for 20 h, then concentrated. The residue was eluted from a column of silica gel with cyclohexane−AcOEt (from 2:1 to 1:1) to give **22** (51 mg, 73%) as a syrup. ^{1}H NMR (300 MHz, DMSO-d_6, 120 °C) (selected data) δ 5.22−5.03 (m, 3 H, H-6, H-7, H-8), 4.08−3.64 (m, 5 H, 2 H-1, H-2, H-5, H-9), 2.11, 2.02, and 1.97 (3 s, 9 H, 3 Ac), 1.46 (s, 9 H, *t*-Bu); MALDI-TOF MS (501.58) 524.3 (M^+ + Na), 540.5 (M^+ + K). Anal. Calcd for $C_{24}H_{39}NO_{10}$: C, 57.47; H, 7.84; N, 2.79. Found: C, 57.20; H, 7.63; N, 2.88.

Methyl 6,7,8-Tri-*O*-acetyl-5,9-anhydro-2-*tert*-butoxycarbonylamino-2,3,4,10-tetradeoxy-L-*threo*-D-*gulo*- and -D-*ido*-deconate (23). To a stirred, cooled (0 °C) solution of **22** (91 mg, 0.16 mmol) in acetone (3 mL) was added freshly prepared 1 M Jones' reagent (480 μL, 0.48 mmol). The mixture was allowed to warm to rt in 30 min, stirred at rt for an additional 2.5 h, diluted with 2-propanol (∼0.5 mL), then with brine (10 mL), and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. Treatment of a solution of crude acid in 1:1 Et_2O−MeOH with ethereal diazomethane at 0 °C for 5 min gave, after column chromatography on silica gel (1:1 cyclohexane−AcOEt), **23** (55 mg, 70%) as a ca. 3:2 mixture of C-2 epimers. ^{1}H NMR (300 MHz) (selected data) δ 5.32 (dd, 1 H, $J_{5,6}$ = 5.6 Hz, $J_{6,7}$ = 10.2 Hz, H-6), 5.28 (dd, 1 H, $J_{7,8}$ = 3.3 Hz, $J_{8,9}$ = 1.6 Hz, H-8), 5.18 (dd, 0.4 H, H-7), 5.17 (dd, 0.6 H, H-7), 4.22−4.12 (m, 1 H, H-5), 3.92 (dq, 0.4 H, $J_{9,10}$ = 6.5 Hz, H-9), 3.90 (dq, 0.6 H, $J_{9,10}$ = 6.5 Hz, H-9), 3.77 (s, 3 H, OMe), 1.47 (s, 1.8 H, *t*-Bu), 1.46 (s, 1.2 H, *t*-Bu), 1.17 (d, 3 H, 3 H-10); MALDI-TOF MS (489.53) 512.3 (M^+ + Na), 528.3 (M^+ + K). Anal. Calcd for $C_{22}H_{35}NO_{11}$: C, 53.98; H, 7.21; N, 2.86. Found: C, 53.66; H, 7.17; N, 2.98.

3-*tert*-Butoxycarbonylamino-2,3-dideoxy-3,4-*N*,*O*-isopropylidene-*aldehydo*-D-*glycero*-tetrose (24). A mixture of (*S*)-*N*-*tert*-butoxycarbonyl-4-(2-hydroxyethyl)-2,2-dimethyloxazolidine[58,59] (500 mg, 2.04 mmol; crystallized from cyclohexane, mp 73−75 °C), activated 4 Å powdered molecular sieves (2.0 g), and anhydrous CH_2Cl_2 (10 mL) was stirred at rt for 10 min, and then pyridinium chlorochromate (2.15 g, 10.0 mmol) was added. The suspension was vigorously stirred for 40 min, then diluted with Et_2O (10 mL) and cyclohexane (10 mL), stirred for an additional 5 min, and filtered through a short pad of silica gel (7 × 2 cm, d × h) placed in a syntherized glass filter and previously conditioned in 1:1 Et_2O−cyclohexane. Further elution with 1:1 Et_2O−cyclohexane (ca. 200 mL) gave pure **24** (390 mg, 79%) as a white solid that could not be recrystallized (mp <40 °C). $[\alpha]_D$ +34.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, DMSO-d_6, 100 °C) δ 9.70 (dd, 1 H, $J_{1,2a}$ = 2.2 Hz, $J_{1,2b}$ = 1.8 Hz, H-1), 4.25 (dddd, 1 H, $J_{2a,3}$ = 5.3 Hz, $J_{2b,3}$ = 7.0 Hz, $J_{3,4a}$ = 6.0 Hz, $J_{3,4b}$ = 2.2 Hz, H-3), 4.04 (dd, 1 H, $J_{4a,4b}$ = 9.2 Hz, H-4a), 3.73 (dd, 1 H, H-4b), 2.75 (ddd, 1 H, $J_{2a,2b}$ = 16.0 Hz, H-2a), 2.66 (ddd, 1 H, H-2b), 1.51 and 1.45 (2 s, 6 H, 2 Me), 1.44 (s, 9 H, *t*-Bu). Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.02; H, 8.63; N, 5.85.

6,10-Anhydro-7,8,9-tri-*O*-benzyl-2-*tert*-butoxycarbonylamino-2,3,4,5,11-pentadeoxy-1,2-*N*,*O*-isopropylidene-L-*threo*-D-*ido*-undec-4-(*Z*)-enitol (25). A mixture of phosphonium salt **19** (760 mg, 0.92 mmol), activated 4-Å powdered molecular sieves (0.90 g), anhydrous THF (7.1 mL), and anhydrous HMPA (4.7 mL) was stirred at room temperature for 10 min, then cooled to −20 °C. The stirred mixture was treated with *n*-butyllithium (580 μL, 0.92 mmol of a 1.6 M solution in hexanes), warmed to 0 °C, stirred for an additional 30 min, and then cooled to −20 °C. To the stirred mixture was added a solution of **24** (336 mg, 1.37 mmol) in anhydrous THF (7.1 mL) over a 15-min period. The mixture was allowed to reach 0 °C in 2.5 h, stirred at 0 °C for an additional 60 min, then diluted with Et_2O (200 mL), and filtered through a pad of Celite. The ethereal solution was washed with 1 M phosphate buffer at pH 7 (3 × 30 mL), dried (Na_2SO_4), and concentrated. The residue was eluted from a column of silica gel with 5:1 cyclohexane−AcOEt to give **25** (457 mg, 75%) as a syrup. $[\alpha]_D$ −1.1 (*c* 1.4, $CHCl_3$); ^{1}H NMR (300 MHz, DMSO-d_6, 160 °C) (selected data) δ 5.83 (dddd, 1 H, J = 1.5, 1.5, 7.5, 11.5 Hz, CH═), 5.69−5.60 (m, 1 H, CH═), 4.78 and 4.58 (2 d,

2 H, J = 11.9 Hz, PhCH_2), 4.76 and 4.71 (2 d, 2 H, J = 11.5 Hz, PhCH_2), 4.63 and 4.57 (2 d, 2 H, J = 11.7 Hz, PhCH_2), 1.50 and 1.44 (2 s, 6 H, 2 Me), 1.44 (s, 9 H, *t*-Bu), 1.19 (d, 3 H, $J_{10,11}$ = 6.4 Hz, 3 H-11). Anal. Calcd for $C_{40}H_{51}NO_7$: C, 73.03; H, 7.81; N, 2.13. Found: C, 72.78; H, 7.72; N, 2.29.

7,8,9-Tri-*O*-acetyl-6,10-anhydro-2-*tert*-butoxycarbonylamino-2,3,4,5,11-pentadeoxy-1,2-*N*,*O*-isopropylidene-L-*threo*-D-*ido*-undecitol (27). The alkene **25** (190 mg, 0.28 mmol) was hydrogenated and acetylated as described for the preparation of **22** to give, after column chromatography on silica gel (2.5:1 cyclohexane−AcOEt), first **27** (82 mg, 55%) as a syrup. $[\alpha]_D$ −45.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, DMSO-d_6, 120 °C) δ 5.22−5.15 (m, 2 H, H-8, H-9), 5.10 (dd, 1 H, $J_{6,7}$ = 5.3 Hz, $J_{7,8}$ = 9.3 Hz, H-7), 4.09−4.01 (m, 2 H, H-6, H-10), 3.93 (dd, 1 H, $J_{1a,1b}$ = 8.8 Hz, $J_{1a,2}$ = 6.0 Hz, H-1a), 3.80 (dddd, 1 H, $J_{1b,2}$ = 1.9 Hz, $J_{2,3a}$ = 4.0 Hz, $J_{2,3b}$ = 8.0 Hz, H-2), 3.68 (dd, 1 H, H-1b), 2.10, 2.03, and 1.96 (3 s, 9 H, 3 Ac), 1.51 and 1.44 (2 s, 6 H, 2 Me), 1.46 (s, 9 H, *t*-Bu), 1.09 (d, 3 H, $J_{10,11}$ = 6.5 Hz, 3 H-11). Anal. Calcd for $C_{25}H_{41}NO_{10}$: C, 58.24; H, 8.02; N, 2.72. Found: C, 58.02; H, 7.91; N, 2.73.

Eluted second was **26** (22 mg, 15%) as a syrup. $[\alpha]_D$ −48.9 (*c* 0.8, $CHCl_3$); ^{1}H NMR (300 MHz) δ 5.32 (dd, 1 H, $J_{6,7}$ = 5.7 Hz, $J_{7,8}$ = 10.2 Hz, H-7), 5.27 (dd, 1 H, $J_{8,9}$ = 3.2 Hz, $J_{9,10}$ = 1.7 Hz, H-9), 5.21 (dd, 1 H, H-8), 4.53 (bd, 1 H, $J_{2,NH}$ = 8.5 Hz, NH), 4.19 (ddd, 1 H, $J_{5a,6}$ = 3.1 Hz, $J_{5b,6}$ = 11.4 Hz, H-6), 4.14−4.01 (m, 2 H), 3.93 (dq, 1 H, $J_{10,11}$ = 6.4 Hz, H-10), 3.91−3.82 (m, 1 H), 2.18, 2.09, 2.08, and 2.02 (4 s, 12 H, 4 Ac), 1.43 (s, 9 H, *t*-Bu), 1.16 (d, 3 H, 3 H-11). Anal. Calcd for $C_{24}H_{39}NO_{11}$: C, 55.69; H, 7.60; N, 2.71. Found: C, 55.41; H, 7.48; N, 2.85.

Methyl 7,8,9-Tri-*O*-acetyl-6,10-anhydro-2-*tert*-butoxycarbonylamino-2,3,4,5,11-pentadeoxy-L-*threo*-D-*ido*-undeconate (28). Compound **27** (100 mg, 0.19 mmol) was oxidized and methylated as described for the preparation of **23** to give, after column chromatography on silica gel (2:1 cyclohexane−AcOEt), **28** (71 mg, 73%) as a foam. $[\alpha]_D$ −52.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz) δ 5.28 (dd, 1 H, $J_{6,7}$ = 5.7 Hz, $J_{7,8}$ = 10.2 Hz, H-7), 5.24 (dd, 1 H, $J_{8,9}$ = 3.4 Hz, $J_{9,10}$ = 1.8 Hz, H-9), 5.17 (dd, 1 H, H-8), 5.01 (bd, 1 H, $J_{2,NH}$ = 8.5 Hz, NH), 4.30 (ddd, 1 H, $J_{2,3a}$ = 4.7 Hz, $J_{2,3b}$ = 7.8 Hz, H-2), 4.16 (ddd, 1 H, $J_{5a,6}$ = 3.2 Hz, $J_{5b,6}$ = 11.5 Hz, H-6), 3.90 (dq, 1 H, $J_{10,11}$ = 6.5 Hz, H-10), 3.74 (s, 3 H, OMe), 2.15, 2.05, and 2.00 (3 s, 9 H, 3 Ac), 1.43 (s, 9 H, *t*-Bu), 1.13 (d, 3 H, 3 H-11). Anal. Calcd for $C_{23}H_{37}NO_{11}$: C, 54.86; H, 7.41; N, 2.78. Found: C, 54.63; H, 7.30; N, 2.86.

2,6-Anhydro-3,4,5-tri-*O*-benzyl-7-deoxy-1-*C*-phenyl-*aldehydo*-L-*glycero*-D-*manno*-heptose (31). To a cooled (−60 °C), stirred solution of β-**1** (290 mg, 0.64 mmol) in anhydrous THF (6.4 mL) was added dropwise a solution of commercially available phenylmagnesium bromide (430 μL, 1.29 mmol,of a 3.0 M solution in Et_2O) over a 15-min period. The solution was allowed to warm to −35 °C in 1.5 h, then poured into 20 mL of a 1 M phosphate buffer at pH 7, and extracted with Et_2O (2 × 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. A mixture of the crude alcohols, activated 4-Å powdered molecular sieves (0.6 g), and anhydrous CH_2Cl_2 (9 mL) was stirred at rt for 10 min, and then pyridinium chlorochromate (0.69 g, 3.20 mmol) was added. The suspension was vigorously stirred for 60 min, then diluted with Et_2O (40 mL) and cyclohexane (20 mL), stirred for an additional 5 min, and filtered through a short pad of silica gel (3 × 1 cm, d × h) placed in a syntherized glass filter and previously conditioned in 1:1 Et_2O−cyclohexane. Further elution with 1:1 Et_2O−cyclohexane (ca. 100 mL) gave crude **31** (0.30 g). The residue was eluted from a column of silica gel with 6:1 cyclohexane−AcOEt to give **31** (225 mg, 67% from β-**1**) as a white solid. Mp 142−143 °C (cyclohexane); $[\alpha]_D$ −16.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz) δ 8.15−8.11 (m, 2 H, 2 H_{ortho} of Ph), 7.53 (tt, 1 H, J = 1.2, 7.4 Hz, H_{para} of Ph), 7.43−7.28, 7.20−7.16, and 7.10−7.07 (3 m, 17 H, Ar), 5.08 and 4.73 (2 d, 2 H, J = 11.6 Hz, PhCH_2), 4.81 and 4.77 (2 d, 2 H, J = 11.9 Hz, PhCH_2), 4.76 and 4.56 (2 d, 2 H, J = 10.2 Hz, PhCH_2), 4.47−4.44 (m, 2 H), 3.78−3.72 (m, 2 H), 3.67 (dq, 1 H, $J_{5,6}$ = 0.6 Hz, $J_{6,7}$ = 6.4 Hz, H-6), 1.24 (d, 3 H, 3 H-7). Anal. Calcd for $C_{34}H_{34}O_5$: C, 78.14; H, 6.56. Found: C, 77.83; H, 6.43.

(1*R*)-2,6-Anhydro-3,4,5-tri-*O*-benzyl-7-deoxy-1-*C*-phenyl-1-*C*-(2-thiazolyl)-L-*glycero*-D-*manno*-heptitol (32). To a cooled (−78 °C), stirred solution of *n*BuLi (600 μL, 0.95 mmol of a 1.6 M solution in hexane) in anhydrous Et_2O (1.3 mL) was added dropwise a solution of freshly distilled 2-bromothiazole (85 μL, 0.92 mmol) in anhydrous Et_2O (0.5 mL) over a 15-min period. The yellow solution was stirred at −75 °C for 30 min, then a solution of ketone **31** (190 mg, 0.36 mmol) in anhydrous THF (1 mL) was added slowly (10 min). After an additional 30 min at −75 °C the mixture was allowed to warm to −65 °C in 40 min and then poured into 20 mL of a 1 M phosphate buffer at pH 7. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was eluted from a column of silica gel with cyclohexane−AcOEt (from 4:1 to 2:1) to give **32** (165 mg, 75%) as a syrup. $[\alpha]_D$ −69.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz) δ 7.85−7.81 (m, 2 H, Ar), 7.74 and 7.17 (2 d, 2 H, J = 3.3 Hz, Th), 7.39−7.18 and 7.15−7.07 (2 m, 16 H, Ar), 6.78−6.74 (m, 2 H, Ar), 4.99 and 4.63 (2 d, 2 H, J = 11.6 Hz, PhCH_2), 4.80 (s, 1 H, OH), 4.68 and 4.55 (2 d, 2 H, J = 11.5 Hz, PhCH_2), 4.62 (d, 1 H, $J_{2,3}$ = 8.9 Hz, H-2), 4.50 and 3.51 (2 d, 2 H, J = 10.6 Hz, PhCH_2), 4.10 (dd, 1 H, $J_{3,4}$ = 8.9 Hz, H-3), 3.72 (dd, 1 H, $J_{4,5}$ = 2.6 Hz, H-4), 3.67−3.61 (m, 2 H, H-5, H-6), 1.05 (d, 3 H, $J_{6,7}$ = 6.4 Hz, 3 H-7). Anal. Calcd for $C_{37}H_{37}NO_5S$: C, 73.12; H, 6.14; N, 2.30. Found: C, 72.86; H, 6.08; N, 2.45.

3,7-Anhydro-2,4,5,6-tetra-*O*-benzyl-8-deoxy-2-*C*-phenyl-*aldehydo*-L-*threo*-D-*gulo*-octose (33). To a stirred solution of **32** (110 mg, 0.18 mmol) in DMF (0.6 mL) was added NaH (15 mg, 0.36 mmol of a 60% dispersion in oil) and, after 15 min, benzyl bromide (27 μL, 0.23 mmol). The mixture was stirred at rt for 3.5 h, then treated with CH_3OH (0.5 mL), stirred for an additional 10 min, diluted with H_2O (10 mL), and extracted with Et_2O (2 × 40 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. The residue was eluted from a column of silica gel with 3:1 cyclohexane−AcOEt to give (1*R*)-2,6-anhydro-1,3,4,5-tetra-*O*-benzyl-7-deoxy-1-*C*-phenyl-1-*C*-(2-thiazolyl)-L-*glycero*-D-*manno*-heptitol (**32**-Bn) as a syrup (123 mg). ^{1}H NMR (300 MHz, $CDCl_3$, 55 °C) δ 7.78 (d, 1 H, J = 3.2 Hz, Th), 7.74−7.69 (m, 2 H, Ar), 7.42−7.00 (m, 22 H, Ar, Th), 6.51−6.46 (m, 2 H, Ar), 5.26 and 4.84 (2 d, 2 H, J = 12.4 Hz, PhCH_2), 5.02 and 4.63 (2 d, 2 H, J = 11.4 Hz, PhCH_2), 4.88 (d, 1 H, $J_{2,3}$ = 9.2 Hz, H-2), 4.70 and 4.60 (2 d, 2 H, J = 11.8 Hz, PhCH_2), 4.56 and 4.19 (2 d, 2 H, J = 11.2 Hz, PhCH_2), 4.29 (dd, 1 H, $J_{3,4}$ = 8.8 Hz, H-3), 3.83 (dq, 1 H, $J_{5,6}$ = 0.8 Hz, $J_{6,7}$ = 6.5 Hz, H-6), 3.77 (dd, 1 H, $J_{4,5}$ = 2.8 Hz, H-4), 3.75 (dd, 1 H, H-5), 1.30 (d, 3 H, 3 H-7). A solution of **32**-Bn (123 mg, 0.17 mmol) and methyl triflate (29 μL, 0.25 mmol) in anhydrous CH_3CN (1.7 mL) was kept at rt for 10 min, then concentrated. To a stirred suspension of the crude *N*-methylthiazolium salt in CH_3OH (1.7 mL) was added $NaBH_4$ (16 mg, 0.42 mmol). The mixture was stirred at rt for an additional 45 min, diluted with acetone, filtered through a pad of Celite, and concentrated. A solution of the residue in CH_2Cl_2 (50 mL) was washed with 1 M phosphate buffer at pH 7 (10 mL), dried (Na_2SO_4), and concentrated. To a vigorously stirred solution of the thiazolidines in CH_3CN (2 mL) was added dropwise H_2O (0.2 mL) and then $AgNO_3$ in one portion (43 mg, 0.25 mmol). The mixture was stirred at rt for 10 min, then diluted with 1 M phosphate buffer at pH 7 (5 mL) and partially concentrated to remove CH_3CN (bath temperature not exceeding 40 °C). The suspension was extracted with Et_2O (50 mL) and then CH_2Cl_2 (50 mL), and the combined organic phases were dried (Na_2SO_4) and concentrated to give a yellow syrup. A solution of the residue in Et_2O (ca. 50 mL) was filtered through a pad of Celite (1 × 3 cm, h × d) and concentrated to give **33** (58 mg, 50% from **32**) as a colorless syrup ca. 95% pure by ^{1}H NMR analysis. ^{1}H NMR (300 MHz) δ 9.70 (s, 1 H, H-1), 7.75−7.70 (m, 2 H, Ar), 7.43−7.24 (m, 18 H, Ar), 7.14−7.01 (m, 3 H, Ar), 6.42−6.37 (m, 2 H, Ar), 5.25 and 5.08 (2 d, 2 H,

J = 12.0 Hz, PhCH_2), 5.07 and 4.67 (2 d, 2 H, J = 11.3 Hz, PhCH_2), 4.74 and 4.66 (2 d, 2 H, J = 11.6 Hz, PhCH_2), 4.63 (d, 1 H, $J_{3,4}$ = 9.2 Hz, H-3), 4.51 and 4.20 (2 d, 2 H, J = 10.2 Hz, PhCH_2), 4.26 (dd, 1 H, $J_{4,5}$ = 9.5 Hz, H-4), 3.76−3.70 (m, 2 H, H-5, H-6), 3.66 (dq, 1 H, $J_{6,7}$ = 0.6 Hz, $J_{7,8}$ = 6.4 Hz, H-7), 1.32 (d, 3 H, 3 H-8).

Methyl 3,7-Anhydro-2,4,5,6-tetra-*O*-benzyl-8-deoxy-2-*C*-phenyl-L-*threo*-D-*gulo*-octonate (34). To a stirred, cooled (0 °C) solution of **33** (43 mg, 0.07 mmol) in acetone (1.2 mL) was added freshly prepared 1 M Jones' reagent (210 μL, 0.21 mmol). The mixture was allowed to warm to rt in 30 min, stirred at rt for an additional 3 h, diluted with 2-propanol (∼0.2 mL), then with brine (10 mL), and extracted with AcOEt (3 × 25 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. Treatment of a solution of crude acid in 1:1 Et_2O−MeOH with ethereal diazomethane at 0 °C for 5 min gave, after column chromatography on silica gel (3:1 cyclohexane−AcOEt), **34** (32 mg, 72%) as syrup. $[\alpha]_D$ −74.3 (*c* 0.7, $CHCl_3$); ^{1}H NMR (400 MHz) δ 7.84−7.80 (m, 2 H, Ar), 7.41−7.16 (m, 18 H, Ar), 7.09−6.97 (m, 3 H, Ar), 6.36−6.32 (m, 2 H, Ar), 5.26 and 5.12 (2 d, 2 H, J = 12.1 Hz, PhCH_2), 5.04 and 4.63 (2 d, 2 H, J = 11.1 Hz, PhCH_2), 4.70 and 4.62 (2 d, 2 H, J = 11.6 Hz, PhCH_2), 4.60 (d, 1 H, $J_{3,4}$ = 9.2 Hz, H-3), 4.40 and 4.03 (2 d, 2 H, J = 10.2 Hz, PhCH_2), 4.17 (dd, 1 H, $J_{4,5}$ = 8.8 Hz, H-4), 3.72−3.67 (m, 2 H, H-5, H-6), 3.67 (s, 3 H, OMe), 3.61 (dq, 1 H, $J_{6,7}$ = 0.6 Hz, $J_{7,8}$ = 6.4 Hz, H-7), 1.28 (d, 3 H, 3 H-8). Anal. Calcd for $C_{43}H_{44}O_7$: C, 76.76; H, 6.59. Found: C, 76.68; H, 6.50.

2,6-Anhydro-3,4,5-tri-*O*-benzyl-7-deoxy-1-*C*-(2-thiazolyl)-*aldehydo*-L-*glycero*-D-*manno*-heptose (36). To a stirred solution of β-**1** (826 mg, 1.85 mmol) in anhydrous CH_2Cl_2 (9.2 mL) was added dropwise 2-TST **35** in three portions (350 μL, 2.20 mmol, each) every 12 h. The solution was kept at rt for an additional 24 h, then concentrated. To a solution of the crude silyl ethers in freshly distilled DMSO (33 mL) was added freshly distilled acetic anhydride (7 mL). The solution was kept at rt for an additional 50 h, then diluted with saturated aqueous $NaHCO_3$ until pH 7 (ca. 50 mL), and extracted with Et_2O (200 mL). The organic phase was dried (Na_2SO_4) and concentrated. The residue was eluted from a column of silica gel with 3:1 cyclohexane−AcOEt to give **36** (703 mg, 72%) as a white solid. Mp 102−104 °C (cyclohexane); $[\alpha]_D$ +17.8 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz) δ 8.04 and 7.70 (2 d, 2 H, J = 3.0 Hz, Th), 7.41−7.28 (m, 10 H, 2 Ph), 7.18−7.14 and 6.99−6.96 (2 m, 5 H, Ph), 5.13 (d, 1 H, $J_{2,3}$ = 9.6 Hz, H-2), 5.03 and 4.75 (2 d, 2 H, J = 12.0 Hz, PhCH_2), 4.85 and 4.55 (2 d, 2 H, J = 11.8 Hz, PhCH_2), 4.79 and 4.76 (2 d, 2 H, J = 11.9 Hz, PhCH_2), 4.41 (dd, 1 H, $J_{3,4}$ = 9.6 Hz, H-3), 3.81 (dd, 1 H, $J_{4,5}$ = 2.8 Hz, H-4), 3.75−3.69 (m, 2 H, H-5, H-6), 1.20 (d, 3 H, $J_{6,7}$ = 6.3 Hz, 3 H-7). Anal. Calcd for $C_{31}H_{31}NO_5S$: C, 70.30; H, 5.90; N, 2.64. Found: C, 70.25; H, 5.78; N, 2.71.

(1*S*)-2,6-Anhydro-3,4,5-tri-*O*-benzyl-7-deoxy-1-*C*-phenyl-1-*C*-(2-thiazolyl)-L-*glycero*-D-*manno*-heptitol (37). To a cooled (−50 °C), stirred solution of **36** (330 mg, 0.62 mmol) in anhydrous THF (6.2 mL) was added dropwise a solution of commercially available phenylmagnesium bromide (510 μL, 1.55 mmol of a 3.0 M solution in Et_2O) over a 15-min period. The solution was allowed to warm to −30 °C in 1 h, stirred for an additional 1 h at −30 °C, then poured into 20 mL of a 1 M phosphate buffer at pH 7, and extracted with Et_2O (2 × 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was eluted from a column of silica gel with 2:1 cyclohexane−AcOEt to give **37** (375 mg, 99%) as a white solid. Mp 158−159 °C (AcOEt−cyclohexane); $[\alpha]_D$ −63.2 (*c* 0.9, $CHCl_3$); ^{1}H NMR (400 MHz) δ 7.98−7.94 (m, 2 H, Ar), 7.70 (d, 1 H, J = 3.2 Hz, Th), 7.39−7.24 (m, 16 H, Ar, Th), 7.14−7.10 (m, 3 H, Ar), 5.11 (s, 1 H, OH), 4.99 and 4.59 (2 d, 2 H, J = 11.6 Hz, PhCH_2), 4.83 and 4.04 (2 d, 2 H, J = 10.6 Hz, PhCH_2), 4.74 and 4.63 (2 d, 2 H, J = 11.7 Hz, PhCH_2), 4.21 (d, 1 H, $J_{2,3}$ = 9.4 Hz, H-2), 4.10 (dd, 1 H, $J_{3,4}$ = 9.2 Hz, H-3), 3.77 (dd, 1 H, $J_{4,5}$ = 2.5 Hz, H-4), 3.68 (dd, 1 H, $J_{5,6}$ = 0.6 Hz, H-5), 3.53 (dq, 1 H, $J_{6,7}$ = 6.1 Hz, H-6), 1.13 (d, 3 H, 3 H-7). Anal. Calcd for $C_{37}H_{37}NO_5S$: C, 73.12; H, 6.14; N, 2.30. Found: C, 72.88; H, 6.05; N, 2.42.

3,7-Anhydro-2,4,5,6-tetra-*O*-benzyl-8-deoxy-2-*C*-phenyl-*aldehydo*-L-*threo*-D-*ido*-octose (38). To a stirred solution of **37** (320 mg, 0.52 mmol) in DMF (1.7 mL) was added NaH (44 mg, 1.05 mmol of a 60% dispersion in oil) and, after 15 min, benzyl bromide (120 μL, 0.67 mmol). The mixture was stirred at rt for 1 h, then treated with CH_3OH (1 mL), stirred for an additional 10 min, diluted with H_2O (50 mL), and extracted with Et_2O (2 × 100 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. The residue was eluted from a column of silica gel with 4:1 cyclohexane−AcOEt to give (1*S*)-2,6-anhydro-1,3,4,5-tetra-*O*-benzyl-7-deoxy-1-*C*-phenyl-1-*C*-(2-thiazolyl)-L-*glycero*-D-*manno*-heptitol (**37**-Bn) as a syrup (330 mg). ^{1}H NMR (400 MHz) δ 7.54−7.51 (m, 2 H, Ar), 7.46 (d, 1 H, J = 3.3 Hz, Th), 7.41−7.09 (m, 21 H, Ar, Th), 6.77−6.73 (m, 3 H, Ar), 5.19 and 4.75 (2 d, 2 H, J = 12.9 Hz, PhCH_2), 5.12 (d, 1 H, $J_{2,3}$ = 9.4 Hz, H-2), 5.02 and 4.60 (2 d, 2 H, J = 11.2 Hz, PhCH_2), 4.80 and 4.46 (2 d, 2 H, J = 11.6 Hz, PhCH_2), 4.69 and 4.60 (2 d, 2 H, J = 11.7 Hz, PhCH_2), 4.33 (dd, 1 H, $J_{3,4}$ = 9.4 Hz, H-3), 3.86 (dd, 1 H, $J_{4,5}$ = 2.6 Hz, H-4), 3.74 (dd, 1 H, $J_{5,6}$ = 0.5 Hz, H-5), 3.71 (dq, 1 H, $J_{6,7}$ = 6.4 Hz, H-6), 1.24 (d, 3 H, 3 H-7). A solution of **37**-Bn (330 mg, 0.47 mmol) and methyl triflate (80 μL, 0.70 mmol) in anhydrous CH_3CN (4.7 mL) was kept at rt for 10 min, then concentrated. To a warmed (60 °C), stirred suspension of the crude *N*-methylthiazolium salt in CH_3CH_2OH (4.7 mL) was added $NaBH_4$ (52 mg, 1.41 mmol). The mixture was stirred at 60 °C for an additional 15 min, then cooled to rt, diluted with acetone, and concentrated. To a vigorously stirred solution of the thiazolidines in CH_2Cl_2 (0.2 mL) and CH_3CN (9 mL) was added dropwise H_2O (0.4 mL) and then $AgNO_3$ in one portion (120 mg, 0.70 mmol). The mixture was stirred at rt for 15 min, then diluted with 1 M phosphate buffer at pH 7 (20 mL), partially concentrated to remove CH_3CN (bath temperature not exceeding 40 °C), and extracted with Et_2O (2 × 50 mL). The combined organic phases were dried (Na_2SO_4) and concentrated to give a yellow syrup. A solution of the residue in Et_2O (ca. 100 mL) was filtered through a pad of Celite (1 × 3 cm, h × d), and concentrated to give **38** (237 mg, 70% from **37**) as a white solid ca. 95% pure by ^{1}H NMR analysis. ^{1}H NMR (300 MHz) δ 9.36 (s, 1 H, H-1), 7.45−7.20 (m, 25 H, 5 Ph), 5.06 and 4.66 (2 d, 2 H, J = 11.3 Hz, PhCH_2), 5.05 and 4.56 (2 d, 2 H, J = 12.1 Hz, PhCH_2), 4.96 and 4.74 (2 d, 2 H, J = 11.0 Hz, PhCH_2), 4.81 and 4.73 (2 d, 2 H, J = 11.6 Hz, PhCH_2), 4.43 (d, 1 H, $J_{3,4}$ = 9.5 Hz, H-3), 4.36 (dd, 1 H, $J_{4,5}$ = 8.8 Hz, H-4), 3.84 (dd, 1 H, $J_{5,6}$ = 2.7 Hz, H-5), 3.77 (dd, 1 H, $J_{6,7}$ = 0.5 Hz, H-6), 3.64 (dq, 1 H, $J_{7,8}$ = 6.4 Hz, H-7), 1.26 (d, 3 H, 3 H-8).

3,7-Anhydro-4,5,6-tri-*O*-benzyl-8-deoxy-2-*C*-phenyl-*aldehydo*-L-*threo*-D-*ido*-octose (40). A solution of **37** (140 mg, 0.23 mmol) and methyl triflate (40 μL, 0.35 mmol) in anhydrous CH_2Cl_2 (0.5 mL) and CH_3CN (1.8 mL) was kept at rt for 15 min, then concentrated. To a solution of the crude *N*-methylthiazolium salt in CH_3CH_2OH (4 mL) was added $NaBH_4$ (25 mg, 0.69 mmol). The mixture was stirred at rt for an additional 15 min, then diluted with acetone, and concentrated. A solution of the residue in CH_2Cl_2 (50 mL) was washed with 1 M phosphate buffer at pH 7 (2 × 10 mL), dried (Na_2SO_4), and concentrated. To a vigorously stirred solution of the thiazolidines in CH_2Cl_2 (0.5 mL) and CH_3CN (1.8 mL) was added dropwise H_2O (0.2 mL) and then $AgNO_3$ in one portion (58 mg, 0.34 mmol). The mixture was stirred at rt for 15 min, then diluted with 1 M phosphate buffer at pH 7 (50 mL), partially concentrated to remove CH_3CN (bath temperature not exceeding 40 °C), and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic phases were dried (Na_2SO_4) and concentrated to give a yellow syrup. The residue was eluted from a column of silica gel with 30:1 CH_2Cl_2−Et_2O to give **40** (103 mg, 81%) as a foam. $[\alpha]_D$ −122.4 (*c* 0.9, $CHCl_3$); ^{1}H NMR (300 MHz) δ 9.54 (s, 1 H, H-1), 7.59−7.54 (m, 2 H, 2 H_{ortho} of Ph), 7.42−7.24 (m, 18 H, Ar), 4.99 and 4.72 (2 d, 2 H, J = 11.9

Hz, PhCH_2), 4.92 and 4.34 (2 d, 2 H, J = 10.3 Hz, PhCH_2), 4.80 and 4.67 (2 d, 2 H, J = 11.7 Hz, PhCH_2), 4.20 (dd, 1 H, $J_{3,4}$ = 9.4 Hz, $J_{4,5}$ = 9.2 Hz, H-4), 4.10 (d, 1 H, H-3), 3.77 (dd, 1 H, $J_{5,6}$ = 2.6 Hz, H-5), 3.68 (dd, 1 H, $J_{6,7}$ = 0.6 Hz, H-6), 3.47 (dq, 1 H, $J_{7,8}$ = 6.4 Hz, H-7), 1.09 (d, 3 H, 3 H-8). Anal. Calcd for $C_{35}H_{36}O_6$: C, 76.06; H, 6.57. Found: C, 75.81; H, 6.46.

Methyl 3,7-Anhydro-4,5,6-tri-*O*-benzyl-8-deoxy-2-*C*-phenyl-L-*threo*-D-*ido*-octonate (41). To a vigorously stirred solution of **40** (83 mg, 0.15 mmol) in CCl_4 (0.5 mL) and CH_3OH (2.5 mL) was added solid KOH (42 mg, 0.75 mmol) and, after 20 min, iodine (142 mg, 1.12 mmol). One more portion of iodine (142 mg) was added after 45 min. Stirring was continued for an additional 45 min, then the resulting purple suspension was treated with solid KOH (42 mg, 0.75 mmol). After 20 min of stirring the reaction mixture turned a pale yellow, thus iodine was added portionwise (2 × 142 mg, 1.12 mmol) after 45 and 90 min. Stirring was continued for an additional 45 min, then the reaction mixture was treated with solid NH_4Cl until pH 8 and concentrated. A suspension of the residue in AcOEt (100 mL) was washed with saturated aqueous NH_4Cl (30 mL), then 20% aqueous $Na_2S_2O_3$ (2 × 30 mL), dried (Na_2SO_4), and concentrated. The residue was eluted from a column of silica gel with $CHCl_3$−Et_2O (from 30:1 to 15:1) to give **41** (61 mg, 70%) as a white solid. Mp 167−169 °C (cyclohexane); $[\alpha]_D$ −56.4 (*c* 1.2, $CHCl_3$); ^{1}H NMR (300 MHz) δ 7.64−7.59 (m, 2 H, 2 H_{ortho} of Ph), 7.40−7.23 (m, 18 H, Ar), 5.09 and 4.53 (2 d, 2 H, J = 10.5 Hz, PhCH_2), 4.96 and 4.70 (2 d, 2 H, J = 12.0 Hz, PhCH_2), 4.80 and 4.71 (2 d, 2 H, J = 11.6 Hz, PhCH_2), 4.35 (dd, 1 H, $J_{3,4}$ = 9.3 Hz, $J_{4,5}$ = 9.5 Hz, H-4), 4.23 (d, 1 H, H-3), 4.04 (br s, 1 H, OH), 3.82 (dd, 1 H, $J_{5,6}$ = 2.8 Hz, H-5), 3.70 (dd, 1 H, $J_{6,7}$ = 1.0 Hz, H-6), 3.48 (dq, 1 H, $J_{7,8}$ = 6.4 Hz, H-7), 3.28 (s, 3 H, OMe), 1.02 (d, 3 H, 3 H-8). Anal. Calcd for $C_{36}H_{38}O_7$: C, 74.21; H, 6.57. Found: C, 74.40; H, 6.43.

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